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Dated 1 April 2003

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Your reference	T1566PV
Patent application number (The Patent Office will fill in this part)	22 MAR 2002 0206876.5

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P01/7700 0.00-0206876.5

Full name, address and postcode of the or of each applicant (underline all surnames)	Merck Sharp & Dohme Limited Hertford Road, Hoddesdon Hertfordshire EN11 9BU United Kingdom
Patents ADP number (if you know it)	00597799001 ✓
If the applicant is a corporate body, give the country/state of its incorporation	United Kingdom
Title of the invention	Therapeutic agents
Name of your agent (if you have one)	Mr. I. J. Hiscock
"Address for service" in the United Kingdom to which all correspondence should be sent including the postcode)	Merck & Co., Inc. European Patent Department Terlings Park Eastwick Road Harlow Essex CM20 2QR
Patents ADP number (if you know it)	06546683001 ✓

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Is a statement of inventorship and of right to grant of a patent required in support of this request? (Answer 'Yes' if:

Yes

a) any applicant named in part 3 is not an inventor, or
b) there is an inventor who is not named as an applicant, or
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I/We request the grant of a patent on the basis of this application.

Signature Date 22 March 2002

Mr. I. J. Hiscock

Name and daytime telephone number of person to contact in the United Kingdom: Mr. I. J. Hiscock - 01279 440175

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THERAPEUTIC AGENTS

The present invention is concerned with heteroaromatic ureas and pharmaceutically acceptable salts and prodrugs thereof which are useful as therapeutic compounds, particularly in the treatment of pain and other conditions ameliorated by the modulation of the function of the vanilloid-1 receptor (VR1).

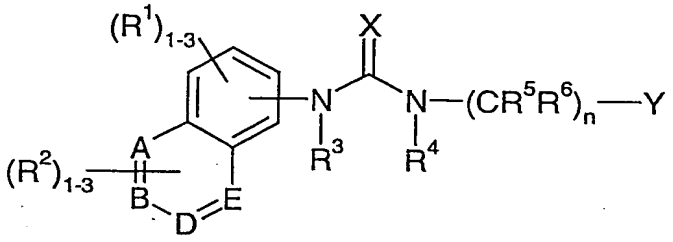
The pharmacologically active ingredient of chilli peppers has been recognised for some time to be the phenolic amide capsaicin. The application of capsaicin to mucous membranes or when injected intradermally, causes intense burning-like pain in humans. The beneficial effects of topical administration of capsaicin as an analgesic is also well established. However, understanding of the underlying molecular pharmacology mediating these responses to capsaicin has been a more recent development.

The receptor for capsaicin, termed the vanilloid VR1 receptor, was cloned by Caterina and colleagues at UCSF in 1997 (*Nature,* **398**:816, 1997). VR1 receptors are cation channels that are found on sensory nerves that innervate the skin, viscera, peripheral tissues and spinal cord. Activation of VR1 elicits action potentials in sensory fibres that ultimately generate the sensation of pain. Importantly VR1 receptor is activated not only by capsaicin by also by acidic pH and by noxious heat stimuli and thus appears to be a polymodal integrator of painful stimuli.

The prototypical VR1 antagonist is capsazepine (Walpole *et al.*, *J. Med. Chem.*, **37**:1942, 1994). This has only micromolar affinity for VR1 and is non-specific in its action. A novel series of sub-micromolar antagonists has also been reported recently (Lee *et al*, *Bioorg. Med. Chem.*, **9**:1713, 2001), but these reports provide no evidence for *in vivo* efficacy. A much higher affinity antagonist has been derived from the 'ultra-potent' agonist resiniferatoxin. Iodo-resiniferatoxin (Wahl *et al., Mol. Pharmacol.*, **59**:9, 2001) is a nanomolar antagonist of VR1 but does not possess properties suitable for an oral pharmaceutical. This last is also true of the micromolar peptoid antagonists described by Garcia-Martinez (*Proc. Natl. Acad. Sci., USA*, **99**:2374, 2002). Most recently International (PCT) patent publication No. WO 02/08221 has described a novel series of VR1 antagonists, which are stated to show efficacy in a number of

animal models. We herein describe another novel series of VR1 modulators. These comprise predominantly VR1 antagonists but encompass VR1 partial antagonists and VR1 partial agonists. Such compounds have been shown to be efficacious in animal models of pain.

The present invention provides compounds of formula (I):



(I)

wherein

A, B, D and E are each C or N with the proviso that one or more are N;

R^1 and R^2 are each independently hydrogen, halogen, hydroxy, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, haloC_{1-6}alkyl, hydroxyC_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkoxy, C_{3-7}cycloalkyl, C_{3-5}cycloalkylC_{1-4}alkyl, NR^7R^8, carboxy, esterified carboxy, C_{1-6}alkyl substituted with a group selected from NR^7R^8, carboxy and esterified carboxy, or C_{1-6}alkoxy substituted with a group selected from NR^7R^8, carboxy and esterified carboxy;

R^3 and R^4 are each independently hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl or C_{2-6}alkynyl;

R^5 and R^6 are, at each occurrence, independently hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, C_{1-6}acyloxy, carboxy, esterified carboxy, $CONR^7R^8$, SO_2R^7, $SO_2NR^7R^8$, aryl, heteroaryl, heterocyclyl, or C_{1-6}alkyl substituted with a group selected from hydroxy, C_{1-6}alkoxy, C_{1-6}acyloxy, carboxy, esterified carboxy, NR^7R^8, $CONR^7R^8$, SR^7, SO_2R^7, $SO_2NR^7R^8$, aryl, heteroaryl and heterocyclyl;

or R^5 and R^6 and the carbon atom to which they are attached together form a carbocyclic ring of 3 to 6 carbon atoms;

R^7 and R^8 are, at each occurrence, independently hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-7}cycloalkyl or fluoroC_{1-6}alkyl;

or R^7 and R^8 and the nitrogen atom to which they are attached together form a heteroaliphatic ring of 4 to 7 ring atoms, optionally substituted by one or two groups selected from hydroxy or C_{1-4}alkoxy, which ring may optionally contain as one of the said ring atoms an oxygen or a sulfur atom, a group S(O) or $S(O)_2$, or a

second nitrogen atom which will be part of a NH or NR^a moiety where R^a is C_{1-4}alkyl optionally substituted by hydroxy or C_{1-4}alkoxy;

X is an oxygen or sulfur atom or the group =NCN;

Y is an aryl, heteroaryl, carbocyclyl or fused-carbocyclyl group; and

n is either zero or an integer from 1 to 3;

or a pharmaceutically acceptable salt, N-oxide or a prodrug thereof.

A preferred class of compound of formula (I) is that wherein R^1 is a hydrogen or halogen atom or a group selected from C_{1-6}alkyl and C_{1-6}alkoxy.

More particularly, a preferred class of compound of formula (I) is that wherein R^1 is a hydrogen or a halogen atom, particularly a hydrogen or a fluorine atom, and most especially a hydrogen atom.

Where R^1 is other than hydrogen, preferably there is only one R^1 substituent.

Another preferred class of compound of formula (I) is that wherein R^2 is a hydrogen or halogen atom or a group selected from C_{1-6}alkyl, haloC_{1-6}alkyl, C_{1-6}alkoxy, NR^7R^8, C_{1-6}alkyl substituted with NR^7R^8, and C_{1-6}alkoxy substituted with NR^7R^8, wherein R^7 and R^8 each independently preferably represent hydrogen atoms or C_{1-4}alkyl groups.

A further preferred class of compound of formula (I) is that wherein R^2 is a hydrogen or a halogen atom, or a group selected from C_{1-4}alkyl, C_{1-4}alkoxy and NR^7R^8, wherein R^7 and R^8 each independently preferably represent hydrogen atoms or C_{1-4}alkyl groups.

More particularly, R^2 preferably represents a hydrogen or chlorine atom or a group selected from methyl, methoxy and dimethylamino. Most preferably, R^2 is a hydrogen atom.

Where R^2 is other than hydrogen, preferably there is only one R^2 substituent.

A further preferred class of compound of formula (I) is that wherein R^3 is a hydrogen atom or a C_{1-4}alkyl group, particularly a hydrogen atom or a methyl group, and most especially a hydrogen atom.

A yet further preferred class of compound of formula (I) is that wherein R^4 is a hydrogen atom or a C_{1-4}alkyl group, particularly a hydrogen atom or a methyl group, and most especially a hydrogen atom.

Another preferred class of compound of formula (I) is that wherein R^5 and R^6 each independently represent a hydrogen atom or a group selected from C_{1-6}alkyl, C_{1-6}alkyl substituted by a group selected from hydroxy, C_{1-6}acyloxy, carboxy, esterified carboxy, NR^7R^8 and heterocyclyl, or an aryl group

More particularly, a preferred class of compound of formula (I) is that wherein R^5 and R^6 each independently represent a hydrogen atom or a C_{1-4}alkyl or phenyl group, particularly a hydrogen atom or a methyl group, and most especially a hydrogen atom.

A further preferred class of compound of formula (I) is that wherein X is an oxygen atom.

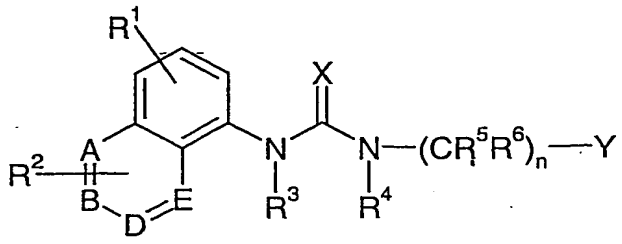
A yet further preferred class of compound of formula (I) is that wherein Y is an aryl group selected from unsubstituted phenyl and phenyl substituted by one or two substituents selected from halogen, C_{1-4}alkyl, C_{1-4}alkoxy, haloC_{1-4}alkyl, haloC_{1-4}alkoxy, phenyl and pyrazolyl; or a heteroaryl group selected from pyridyl, thiazolyl, isoxazolyl, oxadiazolyl and pyrazolyl wherein each heteroaryl group is optionally substituted with one or two substituents selected from C_{1-4}alkyl, C_{1-4}alkoxy, haloC_{1-4}alkyl, haloC_{1-4}alkoxy, phenyl; or a carbocyclyl group which is a C_{5-7}cycloalkyl radical that is unsubstituted or substituted by a phenyl ring; or a fused-carbocyclyl group which is a C_{5-7}cycloalkyl radical that is fused to a phenyl ring.

Another preferred class of compound of formula (I) is that wherein one of A, B, D and E is a nitrogen atom and the other three are carbon atoms, or A and B are nitrogen atoms and D and E are carbon atoms.

It will be appreciated that the group R^2 is attached to any available carbon atom represented by A, B, D and E.

When present, R^7 is preferably a hydrogen atom or a C_{1-4}alkyl group, and R^8 is preferably a hydrogen atom or a C_{1-4}alkyl group, or the group NR^7R^8 represents a heteroaliphatic ring selected from azetidinyl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl or a piperazinyl group substituted on the nitrogen atom by C_{1-4}alkyl optionally substituted by hydroxy or C_{1-4}alkoxy. More preferably, the group NR^7R^8 represents a group selected from $-NH_2$, $-NHCH_3$, $-N(CH_3)_2$, $-NHCH_2CH_3$, $-N(CH)CH_2CH_3$ and $-N(CH_2CH_3)_2$, and most especially, $-N(CH_3)_2$.

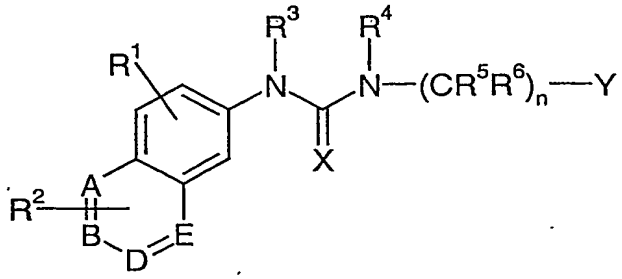
One favoured class of compound of the present invention is that of formula (Ia) and pharmaceutically acceptable salts, N-oxides and prodrugs thereof:



(Ia)

With reference to formula (Ia), preferably E is a carbon atom. Also preferred are those compounds of formula (Ia) where E is a carbon atom, one of A, B and D is a nitrogen atom and the others are carbon atoms, or where A and B are nitrogen atoms and D and E are carbon atoms.

Another favoured class of compound of the present invention is that of formula (Ib) and pharmaceutically acceptable salts, N-oxides and prodrugs thereof:



(Ib)

With reference to formula (Ib), preferably E is a carbon atom. Also preferred are those compounds of formula (Ib) where E is a carbon atom, one of A, B and D is a nitrogen atom and the others are carbon atoms, or where A and B are nitrogen atoms and D and E are carbon atoms. With reference to compounds of formula (Ib), preferably, A is a nitrogen atom and B, D and E are carbon atoms.

When any variable occurs more than one time in formula (I), formula (Ia) or formula (Ib) or in any substituent, its definition on each occurrence is independent of its definition at every other occurrence.

As used herein, the term "alkyl" or "alkoxy" as a group or part of a group means that the group is straight or branched. Examples of suitable alkyl groups include methyl, ethyl, n-propyl, i-propyl, n-butyl, s-butyl and t-butyl. Examples of suitable alkoxy groups include methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, s-butoxy and t-butoxy.

As used herein, the term "hydroxyC_{1-6}alkyl" means a C_{1-6}alkyl group in which one or more (in particular 1 to 3, and especially 1) hydrogen atoms have been replaced by hydroxy groups. Particularly preferred are hydroxyC_{1-3}alkyl groups, for example, CH_2OH, CH_2CH_2OH, $CH(CH_3)OH$ or $C(CH_3)_2OH$, and most especially CH_2OH.

As used herein, the terms "haloC_{1-6}alkyl" and "haloC_{1-6}alkoxy" means a C_{1-6}alkyl or C_{1-6}alkoxy group in which one or more (in particular, 1 to 3) hydrogen atoms have been replaced by halogen atoms, especially fluorine or chlorine atoms. Preferred are fluoroC_{1-6}alkyl and fluoroC_{1-6}alkoxy groups; in particular, fluoroC_{1-3}alkyl and fluoroC_{1-3}alkoxy groups, for example, CF_3, CH_2CH_2F, CH_2CHF_2, CH_2CF_3, OCF_3, OCH_2CH_2F, OCH_2CHF_2 or OCH_2CF_3, and most especially CF_3, OCF_3 and OCH_2CF_3.

The cycloalkyl groups referred to herein may represent, for example, cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl. Suitable C_{3-7}cycloalkylC_{1-4}alkyl groups include, for example, cyclopropylmethyl and cyclohexylmethyl.

Similarly cycloalkoxy groups referred to herein may represent, for example, cyclopropoxy or cyclobutoxy.

As used herein, the terms "alkenyl" and "alkynyl" as a group or part of a group means that the group is straight or branched. Examples of suitable alkenyl groups include vinyl and allyl. A suitable alkynyl group is acetylene or propargyl.

When used herein, the term "halogen" means fluorine, chlorine, bromine and iodine. The most apt halogens are fluorine and chlorine of which fluorine is preferred, unless otherwise stated.

When used herein, the term "carboxy" as a group or part of a group denotes CO_2H.

When used herein, the term "esterified carboxy" denotes a C_{1-6}alkoxy or a haloC_{1-6}alkoxy radical attached via the oxygen atom thereof to a carbonyl (C=O) radical thus forming a C_{1-6}alkoxycarbonyl or haloC_{1-6}alkoxycarbonyl radical.

Suitable examples of such esterified carboxy groups include, for example, methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl and *tert*-butoxycarbonyl.

When used herein, the term "acyloxy" denotes a C_{1-6}alkyl or a haloC_{1-6}alkyl radical attached to a carbonyl (C=O) radical thus forming a C_{1-6}alkoyl or haloC_{1-6}alkanoyl radical which is attached via the carbonyl (C=O) radical to an oxygen atom. Suitable examples of such esterified carboxy groups include, for example, acetoxy, propionyloxy, isopropionyloxy and trifluoroacetoxy.

As used herein, the term "aryl" as a group or part of a group means an aromatic radical such as phenyl, biphenyl or naphthyl, wherein said phenyl, biphenyl or naphthyl group may be optionally substituted by one, two or three groups independently selected from halogen, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, NR^7R^8, benzyl, NO_2, cyano, SR^b, SOR^b, SO_2R^b, COR^b, CO_2R^b, $CONR^bR^c$, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-4}alkoxyC_{1-4}alkyl, $-O(CH_2)_mO-$ or a heteroaromatic group selected from furanyl, pyrrolyl, thienyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, pyridyl or pyridyl substituted by a group selected from halogen, haloC_{1-6}alkyl and haloC_{1-6}alkoxy (where R^b and R^c each independently represent hydrogen, C_{1-4}alkyl, C_{3-5}cycloalkyl or fluoroC_{1-4}alkyl and m is 1 or 2).

Preferably said phenyl, biphenyl or naphthyl group is optionally substituted by one or two substituents, especially none or one. Particularly preferred substituents include fluorine, chlorine, C_{1-4}alkyl (especially methyl or t-butyl), C_{1-4}alkoxy (especially methoxy), trifluoromethyl or trifluoromethoxy.

As used herein, the term "heteroaryl" as a group or part of a group means a 5 or 6-membered monocyclic heteroaromatic radical containing from 1 to 4 nitrogen atoms or an oxygen atom or a sulfur atom, or a combination thereof, or an 8- to 10-membered bicyclic heteroaromatic radical containing from 1 to 4 nitrogen atoms or an oxygen atom or a sulfur atom or a combination thereof. Suitable examples include pyrrolyl, furanyl, thienyl, pyridyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrazinyl, pyrimidinyl, pyridazinyl, triazolyl, oxadiazolyl, thiadiazolyl, triazinyl, tetrazolyl, indolyl, benzofuranyl, benzothiophenyl, benzimidazolyl, benzoxazolyl, benzthiazolyl, benzisothiazolyl, quinolinyl, isoquinolinyl and cinnolinyl, wherein said heteroaromatic radicals may be optionally substituted by one, two or three groups

independently selected from halogen, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, NR^7R^8, phenyl, phenyl substituted by a group selected from halogen, haloC_{1-6}alkyl and haloC_{1-6}alkoxy, benzyl, NO_2, cyano, SR^b, SOR^b, SO_2R^b, COR^b, CO_2R^b, $CONR^bR^c$, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-4}alkoxyC_{1-4}alkyl, $-O(CH_2)_mO-$ or an additional heteroaromatic group selected from furanyl, pyrrolyl, thienyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, pyridyl or pyridyl substituted by a group selected from halogen, haloC_{1-6}alkyl and haloC_{1-6}alkoxy (where R^b, R^c and m are as previously defined).

Preferably said heteroaromatic radical is optionally substituted by one or two substituents, especially none or one. Particularly preferred substituents include C_{1-4}alkyl (especially methyl or *tert*-butyl), C_{1-4}alkoxy (especially methoxy), trifluoromethyl, trifluoromethoxy, phenyl, phenyl substituted by halogen (especially fluorine) and C_{1-4}alkyl (especially methyl), benzyl, or thienyl.

As used herein, the term "carbocyclyl" as a group or part of a group means a 3 to 7-membered cycloalkyl radical such as cyclobutyl, cyclopentyl or cyclohexyl, wherein said cycloalkyl radical may be optionally substituted by one, two or three groups independently selected from halogen, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, NR^7R^8, phenyl, phenyl substituted by a group selected from halogen, haloC_{1-6}alkyl and haloC_{1-6}alkoxy, benzyl, NO_2, cyano, NR^bR^c, SR^b, SOR^b, SO_2R^b, COR^b, CO_2R^b, $CONR^bR^c$, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-4}alkoxyC_{1-4}alkyl, $-O(CH_2)_mO-$ or a heteroaromatic group selected from furanyl, pyrrolyl, thienyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, pyridyl or pyridyl substituted by a group selected from halogen, haloC_{1-6}alkyl and haloC_{1-6}alkoxy (where R^b, R^c and m are as previously defined).

Preferably said carbocyclyl group is optionally substituted by one or two substituents, especially none or one. A particularly preferred substituent is phenyl.

As used herein, the term "fused-carbocyclyl" as a group or part of a group means a 3 to 7-membered cycloalkyl radical such as cyclobutyl, cyclopentyl, cyclohexyl, or cycloheptyl, wherein said cycloalkyl radical is fused to an aryl or heteroaryl group as herein defined. Preferably, said fused-carbocylyl group is attached to the remainder of the molecule via a carbon atom of the cycloalkyl radical. Preferably, said cycloalkyl radical is fused to a phenyl or pyridyl ring

where said phenyl ring is optionally substituted by a group selected from halogen (especially fluorine) and fluoroC_{1-4}alkyl (especially trifluoromethyl), furanyl, pyrrolyl, thienyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, and said pyridyl ring is optionally substituted by a group selected from halogen (especially fluorine) and fluoroC_{1-4}alkyl (especially trifluoromethyl). Preferably said cycloalkyl radical is fused to a phenyl ring.

In a further aspect of the present invention, the compounds of formula (I) may be prepared in the form of a pharmaceutically acceptable salt, especially an acid addition salt.

For use in medicine, the salts of the compounds of formula (I) will be non-toxic pharmaceutically acceptable salts. Other salts may, however, be useful in the preparation of the compounds according to the invention or of their non-toxic pharmaceutically acceptable salts. Suitable pharmaceutically acceptable salts of the compounds of this invention include acid addition salts which may, for example, be formed by mixing a solution of the compound according to the invention with a solution of a pharmaceutically acceptable acid such as hydrochloric acid, fumaric acid, p-toluenesulphonic acid, maleic acid, succinic acid, acetic acid, citric acid, tartaric acid, carbonic acid, phosphoric acid or sulphuric acid. Salts of amine groups may also comprise quaternary ammonium salts in which the amino nitrogen atom carries a suitable organic group such as an alkyl, alkenyl, alkynyl or aralkyl moiety. Furthermore, where the compounds of the invention carry an acidic moiety, suitable pharmaceutically acceptable salts thereof may include metal salts such as alkali metal salts, e.g. sodium or potassium salts; and alkaline earth metal salts, e.g. calcium or magnesium salts.

The salts may be formed by conventional means, such as by reacting the free base form of the compound of formula (I) with one or more equivalents of the appropriate acid in a solvent or medium in which the salt is insoluble, or in a solvent such as water which is removed *in vacuo* or by freeze drying or by exchanging the anions of an existing salt for another anion on a suitable ion exchange resin.

The present invention also includes within its scope N-oxides of the compounds of formula (I) above. In general, such N-oxides may be formed on any available nitrogen atom, and preferably on any one of A, B, D or E where they

represent a nitrogen atom. The N-oxides may be formed by conventional means, such as reacting the compound of formula (I) with oxone in the presence of wet alumina.

The present invention includes within its scope prodrugs of the compounds of formula (I) above. In general, such prodrugs will be functional derivatives of the compounds of formula (I) which are readily convertible *in vivo* into the required compound of formula (I). Conventional procedures for the selection and preparation of suitable prodrug derivatives are described, for example, in "Design of Prodrugs", ed. H. Bundgaard, Elsevier, 1985.

A prodrug may be a pharmacologically inactive derivative of a biologically active substance (the "parent drug" or "parent molecule") that requires transformation within the body in order to release the active drug, and that has improved delivery properties over the parent drug molecule. The transformation *in vivo* may be, for example, as the result of some metabolic process, such as chemical or enzymatic hydrolysis of a carboxylic, phosphoric or sulphate ester, or reduction or oxidation of a susceptible functionality.

The present invention includes within its scope solvates of the compounds of formula (I) and salts thereof, for example, hydrates.

The compounds according to the invention may have one or more asymmetric centres, and may accordingly exist both as enantiomers and as diastereoisomers. It is to be understood that all such isomers and mixtures thereof are encompassed within the scope of the present invention. Furthermore, the compounds of formula (I) may also exist in tautomeric forms and the invention includes within its scope both mixtures and separate individual tautomers.

It will be appreciated that the preferred definitions of the various substituents recited herein may be taken alone or in combination and, unless otherwise stated, apply to the generic formula for compounds of the present invention as well as to the preferred classes of compound represented by formula (Ia) and formula (Ib).

The present invention further provides pharmaceutical compositions comprising one or more compounds of formula (I) in association with a pharmaceutically acceptable carrier or excipient.

Preferably the compositions according to the invention are in unit dosage forms such as tablets, pills, capsules, powders, granules, sterile parenteral solutions or suspensions, metered aerosol or liquid sprays, drops, ampoules, auto-injector devices, suppositories, creams or gels; for oral, parenteral, intrathecal, intranasal, sublingual, rectal or topical administration, or for administration by inhalation or insufflation. Oral compositions such as tablets, pills, capsules or wafers are particularly preferred. For preparing solid compositions such as tablets, the principal active ingredient is mixed with a pharmaceutical carrier, e.g. conventional tabletting ingredients such as corn starch, lactose, sucrose, sorbitol, talc, stearic acid, magnesium stearate, dicalcium phosphate or gums, and other pharmaceutical diluents, e.g. water, to form a solid pre-formulation composition containing a homogeneous mixture of a compound of the present invention, or a pharmaceutically acceptable salt thereof. When referring to these pre-formulation compositions as homogeneous, it is meant that the active ingredient is dispersed evenly throughout the composition so that the composition may be readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules. This solid pre-formulation composition is then subdivided into unit dosage forms of the type described above containing from 0.1 to about 500 mg of the active ingredient of the present invention. Favoured unit dosage forms contain from 1 to 500 mg, for example 1, 5, 10, 25, 50, 100, 300 or 500 mg, of the active ingredient. The tablets or pills of the novel composition can be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action. For example, the tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer that serves to resist disintegration in the stomach and permits the inner component to pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric acids and mixtures of polymeric acids with such materials as shellac, cetyl alcohol and cellulose acetate.

The liquid forms in which the novel compositions of the present invention may be incorporated for administration orally or by injection include aqueous solutions, suitably flavoured syrups, aqueous or oil suspensions, and flavoured emulsions with edible oils such as cottonseed oil, sesame oil, coconut oil or peanut

oil, as well as elixirs and similar pharmaceutical vehicles. Suitable dispersing or suspending agents for aqueous suspensions include synthetic and natural gums such as tragacanth, acacia, alginate, dextran, sodium carboxymethylcellulose, methylcellulose, polyvinyl-pyrrolidone or gelatin.

In the treatment of painful conditions such as those listed below, a suitable dosage level is about 1.0 mg to 15 g per day, preferably about 5.0 mg to 5 g per day, and especially about 20 mg to 2 g day. The compounds may be administered on a regimen of 1 to 4 times per day.

It will be appreciated that the amount of a compound of formula (I) required for use in any treatment will vary not only with the particular compounds or composition selected but also with the route of administration, the nature of the condition being treated, and the age and condition of the patient, and will ultimately be at the discretion of the attendant physician.

The invention further provides a compound of formula (I) as defined above, or a pharmaceutically acceptable salt thereof, for use in treatment of the human or animal body. Preferably, said treatment is for a condition which is susceptible to treatment by modulation (preferably antagonism) of VR1 receptors.

The compounds of the present invention will be of use in the prevention or treatment of diseases and conditions in which pain and/or inflammation predominates, including chronic and acute pain conditions. Such conditions include rheumatoid arthritis; osteoarthritis; post-surgical pain; musculo-skeletal pain, particularly after trauma; spinal pain; myofascial pain syndromes; headache, including migraine, acute or chronic tension headache, cluster headache, temporomandibular pain, and maxillary sinus pain; ear pain; episiotomy pain; burns, and especially primary hyperalgesia associated therewith; deep and visceral pain, such as heart pain, muscle pain, eye pain, orofacial pain, for example, odontalgia, abdominal pain, gynaecological pain, for example, dysmenorrhoea, pain associated with cystitis and labour pain; pain associated with nerve and root damage, such as pain associated with peripheral nerve disorders, for example, nerve entrapment and brachial plexus avulsions, amputation, peripheral neuropathies, tic douloureux, atypical facial pain, nerve root damage, and arachnoiditis; itching conditions including pruritis, itch due to hemodialysis, and contact dermatitis; pain (as well as broncho-constriction and inflammation) due to exposure (e.g. via ingestion, inhalation, or eye contact) of

mucous membranes to capsaicin and related irritants such as tear gas, hot peppers or pepper spray; neuropathic pain conditions such as diabetic neuropathy, chemotherapy-induced neuropathy and post-herpetic neuralgia; "non-painful" neuropathies; complex regional pain syndromes; pain associated with carcinoma, often referred to as cancer pain; central nervous system pain, such as pain due to spinal cord or brain stem damage, low back pain, sciatica and ankylosing spondylitis; gout; scar pain; irritable bowel syndrome; inflammatory bowel disease; urinary incontinence including bladder detrusor hyper-reflexia and bladder hypersensitivity; respiratory diseases including chronic obstructive pulmonary disease (COPD), chronic bronchitis, cystic fibrosis and asthma; autoimmune diseases; and immunodeficiency disorders.

Thus, according to a further aspect, the present invention provides a compound of formula (I) for use in the manufacture of a medicament for the treatment or prevention of physiological disorders that may be ameliorated by modulating VR1 activity.

The present invention also provides a method for the treatment or prevention of physiological disorders that may be ameliorated by modulating VR1 activity, which method comprises administration to a patient in need thereof of an effective amount of a compound of formula (I) or a composition comprising a compound of formula (I).

According to a further or alternative aspect, the present invention provides a compound of formula (I) for use in the manufacture of a medicament for the treatment or prevention of a disease or condition in which pain and/or inflammation predominates.

The present invention also provides a method for the treatment or prevention of a disease or condition in which pain and/or inflammation predominates, which method comprises administration to a patient in need thereof of an effective amount of a compound of formula (I) or a composition comprising a compound of formula (I).

According to a further aspect of the present invention, it may be desirable to treat any of the aforementioned conditions with a combination of a compound according to the present invention and one or more other pharmacologically active agents suitable for the treatment of the specific condition. The compound

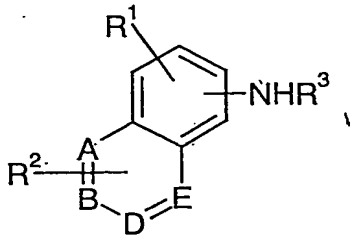
of formula (I) and the other pharmacologically active agent(s) may be administered to a patient simultaneously, sequentially or in combination. Thus, for example, for the treatment or prevention of pain and/or inflammation, a compound of the present invention may be used in conjunction with other analgesics, such as acetaminophen (paracetamol), aspirin and other NSAIDs, including selective cyclooxygenase-2 (COX-2) inhibitors, as well as opioid analgesics, especially morphine, NR2B antagonists, bradykinin antagonists, anti-migraine agents, anticonvulsants such as oxcarbazepine and carbamazepine, antidepressants (such as TCAs, SSRIs, SNRIs, substance P antagonists, etc.), spinal blocks, gabapentin, pregabalin and asthma treatments (such as β_2-adrenergic receptor agonists or leukotriene D_4antagonists (e.g. montelukast).

Specific anti-inflammatory agents include diclofenac, ibuprofen, indomethacin, nabumetone, ketoprofen, naproxen, piroxicam and sulindac, etodolac, meloxicam, rofecoxib, celecoxib, etoricoxib, parecoxib, valdecoxib and tilicoxib. Suitable opioid analgesics of use in conjunction with a compound of the present invention include morphine, codeine, dihydrocodeine, diacetylmorphine, hydrocodone, hydromorphone, levorphanol, oxymorphone, alfentanil, buprenorphine, butorphanol, fentanyl, sufentanyl, meperidine, methadone, nalbuphine, propoxyphene and pentazocine; or a pharmaceutically acceptable salt thereof. Suitable anti-migraine agents of use in conjunction with a compound of the present invention include CGRP-antagonists, ergotamines or 5-HT_1 agonists, especially sumatriptan, naratriptan, zolmatriptan or rizatriptan.

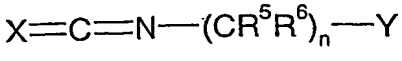
Therefore, in a further aspect of the present invention, there is provided a pharmaceutical composition comprising a compound of the present invention and an analgesic, together with at least one pharmaceutically acceptable carrier or excipient.

In a further or alternative aspect of the present invention, there is provided a product comprising a compound of the present invention and an analgesic as a combined preparation for simultaneous, separate or sequential use in the treatment or prevention of a disease or condition in which pain and/or inflammation predominates.

According to a general process (A), compounds of formula (I) may be prepared by the reaction of a compound of formula (II) with a compound of formula (III):



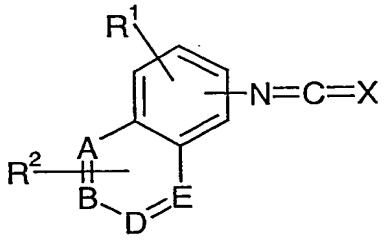
(II)



(III)

The reaction is conveniently effected at a temperature between 20°C and the reflux temperature of the solvent. Suitable solvents include a halogenated hydrocarbon, for example, dichloromethane.

Similarly, according to a general process (B), compounds of formula (I) may also be prepared by the reaction of a compound of formula (IV) with a compound of formula (V):

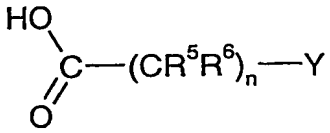


(IV)

(V)

The reaction is essentially effected in the same manner as general process (A).

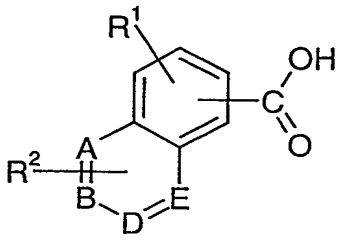
According to an alternative general process (C), compounds of formula (I), in which X is an oxygen atom, may be prepared by the reaction of a compound of formula (II) with a compound of formula (VI):



(VI)

The carboxylic acid is first reacted with diphenylphosphoryl azide and triethylamine which forms the corresponding isocyanate by a Curtius rearrangement. The isocyanate may then be reacted *in situ* with the amine of formula (II) by heating at reflux to give the desired compound of formula (I). The reactions are conveniently effected in a suitable solvent such as an aromatic hydrocarbon, for example, toluene.

Similarly, according to a general process (D), compounds of formula (I), in which X is an oxygen atom, may also be prepared by the reaction of a compound of formula (V) with a compound of formula (VII):



(VII)

The reaction is essentially effected in the same manner as general process (C).

Further details of suitable procedures will be found in the accompanying Examples.

Compounds of formulae (III) and (IV) in which X is an oxygen atom may be prepared in situ, as described in general process (C), or they may be prepared from the corresponding carboxylic acid of formulae (VI) and (VII), respectively, by first being converted into the corresponding acyl halide by reaction with, for example, oxalyl chloride. The acyl halide is then converted into the corresponding acyl azide by reaction with, for example, with sodium azide. The desired isocyanate is then obtained by a conventional Curtius rearrangement by heating the acyl azide at reflux. The reactions are conveniently effected in a suitable solvent such as a halogenated hydrocarbon, for example, dichloromethane.

Compounds of formula (III) and (IV) in which X is a sulfur atom may be prepared from the corresponding amine of formula (IV) and (II), respectively (wherein R^3 and R^4 are hydrogen), by reaction with 1,1'-thiocarbonyl-2(1*H*)-pyridone. The reaction is conveniently effected at room temperature in a suitable solvent such as a halogenated hydrocarbon, for example, dichloromethane.

Compounds of formulae (II) to (VII) are either known compounds or may be prepared by conventional methodology well known to one of ordinary skill in the art using, for instance, procedures described in the accompanying Examples, or by alternative procedures which will be readily apparent.

During any of the above synthetic sequences it may be necessary and/or desirable to protect sensitive or reactive groups on any of the molecules concerned. This may be achieved by means of conventional protecting groups, such as those described in *Protective Groups in Organic Chemistry*, ed. J.F.W. McOmie, Plenum Press, 1973; and T.W. Greene and P.G.M. Wuts, *Protective Groups in Organic Synthesis*, John Wiley & Sons, 1991. The protecting groups may be removed at a convenient subsequent stage using methods known from the art.

The following non-limiting Examples serve to illustrate the preparation of compounds of the present invention:

The structures of the products of the following Descriptions and Examples were in most cases confirmed by ^{1}H NMR.

Description 1

2-Cyano-5-(trifluoromethyl)pyridine

To an ice-cooled solution of 5-(trifluoromethyl)pyridin-2-ol (10.24 g, 62.8 mmol) in anhydrous dichloromethane (200 ml) was added triethylamine (9.63 ml , 69 mmol), followed by dropwise addition of trifluoromethanesulfonic anhydride (12.68 ml , 75.4 mmol). The resulting mixture was stirred at room temperature for 2 hours. The mixture was washed with water (500 ml) and the aqueous layer extracted with dichloromethane (2 x 100 ml). The combined organic layers were washed with water (2 x 300 ml), brine (150 ml), then dried over Na_2SO_4, filtered through a 1 inch plug of silica gel and evaporated. The residue was dissolved in anhydrous N,N-dimethylformamide (150 ml) and zinc cyanide (3.98 g, 33.9 mmol) was added followed by tetrakis(triphenylphosphine)palladium(0) ($Pd(PPh_3)_4$) (3.56 g, 3.09 mmol). The mixture was degassed and heated at 80 °C overnight. The cooled reaction mixture was diluted with water (600 ml) and extracted with ethyl acetate (3 x 150 ml). The combined organic layers were washed with water (2 x 250 ml), brine (150 ml), dried (Na_2SO_4) and evaporated. The residue was purified by column chromatography on silica eluting with a gradient rising from neat iso-hexanes to 10% Et_2O in iso-hexanes to give the title compound (8 g, 75%) as a white solid.

Description 2

2-Aminomethyl-5-(trifluoromethyl)pyridine

To a nitrogen flushed solution of 2-cyano-5-(trifluoromethyl)pyridine (Description 1; 8.0 g, 46.5mmol) in a mixture of ethanol (100 ml) and ammonium hydroxide (25 ml) was added a spatula end of Raney Nickel and the resulting mixture hydrogenated at 50 psi overnight. The catalyst was removed by filtration and the filtrate was evaporated to dryness. The residue was purified by column chromatography on silica eluting with a gradient rising from 2% MeOH in dichloromethane + 0.5% NH_4OH to 5% MeOH in dichloromethane + 0.5% NH_4OH to give the title compound (2.5 g, 30%) as a yellow oil.

Description 3

4-*tert*-Butylpyridine-N-Oxide

To a solution of 4-*tert*-butylpyridine (44.3 ml, 300 mmol) in glacial acetic acid (200 ml) was added hydrogen peroxide (37.1 ml of a 27.5 % aqueous solution, 300 mmol), and the resulting mixture heated at reflux overnight. The cooled mixture was evaporated to dryness. The residue was dissolved in dichloromethane (200 ml), and washed with brine (50 ml), then dried (Na_2SO_4) and evaporated to give the title compound (40 g, 88%) as a white solid.

Description 4

2-Cyano-4-*tert*-butylpyridine

To trimethylsilylcyanide (25.0 ml, 187.5 mmol) was added a solution of 4-*tert*-butylpyridine-N-oxide (Description 3; 22.68 g, 150 mmol) in anhydrous dichloromethane (200 ml). To this mixture was added dropwise a solution of dimethyl carbamoyl chloride (17.26 ml, 187.5 mmol) in anhydrous dichloromethane (50 ml). The reaction mixture was stirred at room temperature for 24 hours. A solution of 10% aqueous K_2CO_3 (200 ml) was added dropwise and the resulting mixture stirred for 10 minutes. The organic layer was separated and the aqueous layer extracted with 2 further portions of dichloromethane (100 ml). The combined organic layers were dried (Na_2SO_4) and evaporated to give the title compound (24 g, 100%).

Description 5

2-Aminomethyl-4-*tert*-butylpyridine

A solution of 2-cyano-4-*tert*-butylpyridine (Description 4; 24.0 g, 150 mmol) was hydrogenated according to the method of Description 2. Following removal of the catalyst, the residue was taken up in dichloromethane (300 ml) and washed with brine, dried over K_2CO_3, filtered and evaporated. The residue was purified by column chromatography on silica eluting with 5% MeOH in dichloromethane + 0.5% NH_4OH to give the title compound (12 g, 48%) as a pale yellow oil.

Description 6

2-[4-(Trifluoromethyl)phenyl]ethylamine

A solution of [4-(trifluoromethyl)phenyl]acetonitrile (9.98 g, 53.9mmol) was hydrogenated according to the method of Description 2. Following removal of the catalyst, the residue was purified by column chromatography on silica eluting with 4% MeOH in dichloromethane + 0.5% NH_4OH to give the title compound (6.5 g, 63%) as an orange oil.

Description 7

3-*tert*-Butylphenyl trifluoromethane sulfonate

To an ice-cooled solution of 3-*tert*-butylphenol (10 g, 66.6 mmol) and triethylamine (13.92 ml, 99.9 mmol) in anhydrous dichloromethane (100 ml) under an atmosphere of nitrogen was added slowly trifluoromethanesulfonic anhydride (12.30 ml, 73.26 mmol), and the resulting mixture stirred at room temperature for 2 hours. The mixture was then washed with 1N HCl (100 ml), brine (100 ml), dried (Na_2SO_4) and evaporated. The residue was purified by column chromatography on silica eluting with iso-hexanes to give the title compound (16.38 g, 87%) as a clear oil.

Description 8

3-*tert*-Butylbenzonitrile

To a solution of 3-*tert*-butylphenyl trifluoromethane sulfonate (Description 7; 16.37 g, 58 mmol) in anhydrous N,N-dimethylformamide (200 ml) was added zinc cyanide (8.17 g, 69.6 mmol), and $Pd(PPh_3)_4$ (3.35 g, 2.9 mmol) and the mixture was then degassed (N_2) and heated at 80 °C overnight. The cooled reaction mixture was poured into water (750 ml), and extracted with ethyl acetate (3 x 200 ml). The combined organic layers were washed with water (2 x 300 ml), brine (200 ml), dried (Na_2SO_4), filtered through a 1 cm plug of silica and evaporated to give the title compound (7 g, 76%).

Description 9

3-*tert*-Butylbenzylamine

A solution of 3-*tert*-butylbenzonitrile (Description 8; 7.0 g, 44 mmol) was hydrogenated according to the method of Description 2. Following removal of the

catalyst, the residue was taken up in dichloromethane (100 ml), washed with brine, dried (Na_2SO_4), filtered through a short plug of silica and evaporated to give the title compound (5.2 g, 72%) as a red oil.

Description 10

2-*tert*-Butyl-5-cyanopyridine

To a mixture of 3-cyanopyridine (10 g, 96 mmol), trimethylacetic acid (9.8 g, 96 mmol) and silver nitrate (1.63 g, 9.6 mmol) in 10% aqueous sulfuric acid (100 ml) at 70°C was added dropwise a solution of ammonium peroxodisulfate (21.9 g, 96 mmol) in water (120 ml). After complete addition the mixture was stirred at 70°C for 2 hours. The mixture was cooled and basified by the addition of 33% aqueous NH_4OH, and extracted with ethyl acetate (3 x 100 ml). The combined organic layers were washed with brine (100 ml), dried (Na_2SO_4) and evaporated to give the title compound (15.6 g, 100%).

Description 11

3-Aminomethyl-6-*tert* butylpyridine

A solution of 2-*tert*-butyl-5-cyanopyridine (Description 10; 15.5 g, 97 mmol) was hydrogenated according to the method of Description 2. Following removal of the catalyst, the residue was purified by column chromatography on silica eluting with 5% MeOH in dichloromethane + 0.5% NH_4OH to give the title compound (10.5 g, 66%), as a pale yellow oil.

Description 12

2-*tert*-Butyl-4-cyanopyridine

A mixture of 4-cyanopyridine (10 g , 96 mmol), trimethylacetic acid (9.8 g, 96 mmol), and silver nitrate (1.63 g , 9.6 mmol) in 10% aqueous sulfuric acid (100 ml) at 70°C was treated with a solution of ammonium peroxodisulfate (21.9 g, 96 mmol) in water (120 ml) according to the method of Description 10. Purification by column chromatography on silica eluting with 10% Et_2O in iso-hexanes gave the title compound (6.5 g, 42%).

Description 13

4-Aminomethyl-2-*tert*-butylpyridine

A solution of 2-*tert*-butyl-4-cyanopyridine (Description 12; 6.50 g, 40.6 mmol) was hydrogenated according to the method of Description 2. Following removal of the catalyst, the residue was taken up in dichloromethane (100 ml), washed with brine, dried (Na_2SO_4), filtered through a short plug of silica and evaporated to give the title compound (6.1 g, 91%) as a brown oil.

Description 14

2-Bromo-6-*tert*-butylpyridine

To potassium *tert*-butoxide (1.0M in *tert* butanol, 100 ml, 100 mmol) was added 2,6-dibromopyridine (15.87 g, 67 mmol), and the resulting mixture heated at reflux for 3.5 hours. The mixture was evaporated and the residue quenched by the addition of water (150 ml). The mixture was extracted with ethyl acetate (3 x 80 ml) and the combined organic layers washed with brine (100 ml), dried (Na_2SO_4) and evaporated. The residue was purified by column chromatography on silica eluting with 2% Et_2O in iso-hexanes to give the title compound (9.9 g, 69%) as a clear oil.

Description 15

2-*tert*-Butyl-6-cyanopyridine

To a solution of 2-bromo-6-*tert*-butylpyridine (Description 14; 9.9 g, 46 mmol) in anhydrous N,N-dimethylformamide (130 ml) was added zinc cyanide (6.48 g, 55.2 mmol) and $Pd(PPh_3)_4$ (2.65 g, 2.3 mmol). The mixture was degassed then heated at 80 °C overnight. The cooled reaction mixture was poured into water (500 ml), and extracted with ethyl acetate (3 x 150 ml). The combined organic layers were washed with water (2 x 300 ml), brine (100 ml), dried (Na_2SO_4) and evaporated. The residue was purified by column chromatography on silica eluting with 5% Et_2O in iso-hexanes to give the title compound (6.6 g, 89%).

Description 16

2-Aminomethyl-6-*tert*-butylpyridine

A solution of 2-*tert*-butyl-6-cyanopyridine (Description 15, 6.6 g, 41.2 mmol) was hydrogenated according to the method of Description 2. Following removal of the

catalyst, the residue was taken up into dichloromethane (300 ml) and washed with brine, dried over K_2CO_3, filtered and evaporated. The residue was purified by column chromatography on silica eluting with 5% MeOH in dichloromethane + 0.5% NH_4OH to give the title compound (4.5 g, 66%) as a pale orange oil.

Description 17

(*E/Z*)-3-[6-(Trifluoromethyl)pyridin-3-yl]prop-2-enenitrile

To an ice-bath cooled suspension of sodium hydride (1.26 g of a 60% dispersion, 31.46 mmol) in anhydrous THF (75 ml) was added dropwise a solution of diethyl cyanomethylphosphonate (5.09 ml, 31.46 mmol) in THF (50 ml). After the addition was complete the mixture was stirred for 10 minutes then a solution of 6-(trifluoromethyl)pyridine-3-carboxaldehyde (5.00 g, 28.6 mmol) in THF (25 ml) was added and the resulting mixture stirred at room temperature for 1 hour. Water (250 ml) was added and the mixture extracted with ethyl acetate (3 x 100 ml). The combined organic layers were washed with water (x2), brine, dried (Na_2SO_4) and evaporated. The residue was purified by column chromatography on silica eluting with a gradient rising from 10% EtOAc in isohexanes to 30% EtOAc in iso-hexanes to give the title compound - E and Z isomers were separated but then re-combined (5.6 g, 100%).

Description 18

3-[6-(Trifluoromethyl)pyridin-3-yl]propylamine

A solution of (*E/Z*)-3-[6-(trifluoromethyl)pyridin-3-yl]prop-2-enenitrile (Description 17; 5.60 g, 28.3mmol) was hydrogenated according to the method of Description 2. Following removal of the catalyst, the residue was purified by column chromatography on silica eluting with 5% MeOH in dichloromethane + 0.5% NH_4OH to give the title compound (3.5 g, 57%).

Description 19

1,2,3,4-Tetrahydronaphthalene-2-carboxamide

To a suspension of 1,2,3,4-tetrahydronaphthalene-2-carboxylic acid (6.08 g, 34.5 mmol) in anhydrous dichloromethane (60 ml) was added oxalyl chloride (4.52 ml, 51.8 mmol), followed by 2 drops of N,N-dimethylformamide and the resulting mixture was stirred at room temperature for 2 hours. The mixture was

evaporated to dryness, toluene (50 ml) was then added and the mixture evaporated to dryness again. The residue was dissolved in anhydrous dichloromethane (100 ml) and added in one portion to dichloromethane (150 ml) which had been saturated with ammonia gas. The resulting mixture was stirred at room temperature for 48 hours. The mixture was evaporated to dryness and the residue partitioned between ethyl acetate (150 ml) and water (250 ml). The aqueous layer was further extracted with ethyl acetate (100 ml). The combined organic layers were washed with water (200 ml), brine (100 ml), then dried (Na_2SO_4) and evaporated to give the title compound (6 g, 99%) as a white solid.

Description 20

1,2,3,4-Tetrahydronaphthalen-2-ylmethylamine

To an ice-bath cooled solution of 1,2,3,4-tetrahydronaphthalene-2-carboxamide (Description 19; 5.99 g, 34.2 mmol) in anhydrous THF (150 ml) was added in portions lithium aluminum hydride (2.6 g, 68.4 mmol). After complete addition, the mixture was heated to reflux for 3 hours then cooled in an ice bath and quenched carefully by the sequential addition of water (2.74 ml), 4N NaOH (2.74 ml) and water (8.2 ml). The resulting suspension was stirred for 10 minutes, then filtered through Celite™ and the filtrate evaporated to give the title compound (4.5 g, 81%).

Description 21

(2*E*/*Z*)-3-[4-(Trifluoromethyl)phenyl]prop-2-enenitrile

To a solution of 4-trifluoromethyliodobenzene (7.23 g, 26.6 mmol) in anhydrous acetonitrile (130 ml) was added triethylamine (3.74 ml, 26.6 mmol), acrylonitrile (1.77 ml, 26.6 mmol), palladium (II) acetate (60 mg, 0.26 mmol), and tri-*o*-tolylphosphine (324 mg, 1.06 mmol) and the resulting mixture heated at reflux overnight. The cooled reaction mixture was filtered through Celite™, and partitioned between water and ethyl acetate. The organic layer was separated and washed with brine, dried (Na_2SO_4) and evaporated. The residue was purified by column chromatography on silica eluting with 5% EtOAc in iso-hexanes to give the title compound (4.07 g, 78%).

Description 22

3-[4-(Trifluoromethyl)phenyl]propylamine

A solution of (2*E*/*Z*)-3-[4-(trifluoromethyl)phenyl]prop-2-enenitrile (Description 21; 4.06 g, 20.6 mmol) was hydrogenated according to the method of Description 2. Following removal of the catalyst, the residue was purified by column chromatography on silica eluting with 4% MeOH in dichloromethane + 0.5% NH_4OH to give the title compound (3.5 g, 83%) as an oil.

Description 23

3-[3-(Trifluoromethyl)phenyl]propylamine

To an ice-bath cooled suspension of sodium hydride (1.32 g of a 60% dispersion in oil, 33 mmol) in anhydrous tetrahydrofuran (100 ml) under a nitrogen atmosphere was added dropwise a solution of diethyl cyanomethylphosphonate (5.34 ml, 33 mmol) in tetrahydrofuran (40 ml) and the resulting mixture stirred at 0 °C for 15 minutes. To this mixture was added a solution of 3-trifluoromethylbenzaldehyde (5.22 g, 30 mmol) in anhydrous tetrahydrofuran (40 ml) and the resulting mixture stirred at room temperature for 1.5 hours. Water (300 ml) was added and the mixture extracted with ethyl acetate (3 x 150 ml). The combined organic layers were washed with water (2 x 200 ml), brine (150 ml) then dried (Na_2SO_4) and evaporated. The residue was taken up in a mixture of ethanol (100 ml) and ammonium hydroxide (25 ml) and hydrogenated according to the method of Description 2. Purification by column chromatography on silica eluting with 5% MeOH in dichloromethane + 0.5% NH_4OH gave the title compound (1.5 g, 25%) as a yellow oil.

Description 24

6-(4-Fluorophenyl)nicotinamide

A mixture of 6-chloronicotinamide (5.00 g, 31.95 mmol), 4-fluorobenzene boronic acid (4.92 g, 35.14 mmol), and $Pd(PPh_3)_4$ (1.10 g, 0.96 mmol) in a mixture of toluene (80 ml), ethanol (12 ml) and 2M sodium carbonate (36.74 ml, 73.48 mmol) was degassed (N_2) and heated at 100 °C for 18 hours. The reaction mixture was cooled to room temperature and then filtered. The collected solid was washed with water and dried. The dried solid was taken up in methanol (100 ml) and heated to reflux for 20 minutes. The mixture was then cooled to room

temperature, filtered and the solid dried to give the title compound (6.25 g, 90%) as a pale grey solid.

Description 25

[6-(4-Fluorophenyl)pyridin-3-yl]methylamine

To an ice-bath cooled solution of sodium borohydride (5.47 g, 144.5 mmol) in anhydrous 1,4-dioxane (100 ml) was added slowly a solution of glacial acetic acid (8.27 ml, 144.5 mmol) in 1,4-dioxane (50 ml). To this mixture was added 6-(4-fluorophenyl)nicotinamide (Description 24; 6.25 g , 28.9 mmol) and the resulting mixture heated at reflux for 4 hours. The cooled reaction mixture was evaporated and water (60 ml) added slowly. This mixture was extracted with dichloromethane, and the solid which appeared between the layers was removed by filtration. This solid was triturated with a mixture of dichloromethane and iso-hexanes, filtered and dried to give the title compound (510 mg, 8%) as a pale green solid.

Description 26

6,7,8,9-Tetrahydro-5*H*-benzo[*a*][7]annulen-6-ylmethylamine hydrochloride

To a nitrogen flushed solution of methyl 6,7-dihydro-5*H*-benzo[*a*][7]annulene-8-carboxylate [*J. Org. Chem.* 1991, **56**, 6199-6205] (54.8 g, 271 mmol) in a mixture of ethyl acetate (250 ml) and glacial acetic acid (5 ml) was added 10% palladium on carbon (10 g) and the mixture was hydrogenated at 55 psi for 16 hours. The catalyst was removed by filtration, and the filtrate evaporated to dryness. The residue was dissolved in ethanol (55 ml) and 3M aqueous NaOH (165 ml, 495 mmol) was added, then the resulting mixture heated to reflux for 2 hours. The mixture was cooled and the ethanol removed by evaporation. The aqueous phase was washed with dichloromethane (x 3) then acidified to pH=1 with 6M HCl and extracted with dichloromethane (x 3). The combined organic phases from the acidic extraction were dried over $MgSO_4$, filtered and evaporated. The residue was triturated with *tert*-butyl methyl ether, filtered and dried to give 6,7,8,9-tetrahydro-5*H*-benzo[*a*][7]annulene-6-carboxylic acid (20.6 g, 40%). This material was dissolved in dichloromethane (100 ml) containing N,N-dimethylformamide (0.5 ml) and oxalyl chloride (9.68 ml, 111 mmol) dropwise at such a rate that the internal temperature did not rise above 10 °C.

The mixture was stirred at 5 °C for 30 minutes, then treated dropwise with 33% aqueous ammonium hydroxide (100 ml) whilst maintaining the temperature below 15 °C. The resulting slurry was then stirred at 10 °C for 30 minutes. The mixture was evaporated and the residue diluted with water and slurried at 0 °C for 15 minutes. The resulting white solids were filtered, washed with more water, hexanes, and dried to give 6,7,8,9-tetrahydro-5*H*-benzo[*a*][7]annulene-6-carboxamide (11.6 g, 55%). This material was dissolved in anhydrous THF and added dropwise over 60 minutes to a slurry of $LiAlH_4$ (3.24 g, 85.4 mmol) in refluxing THF. The reaction was maintained at reflux for 2 hours then cooled to 10 °C, diluted with *tert*-butyl methyl ether, and cautiously quenched by the addition of water while the temperature was maintained below 30 °C. The resulting gummy solid was removed by filtration and the phases were then separated. The aqueous phase was washed with *tert*-butyl methyl ether and the combined organic phases were dried over $MgSO_4$, filtered and evaporated. The residue was dissolved in isopropyl alcohol (30 ml), cooled to 0 °C and concentrated HCl was added dropwise causing a thick slurry to form. The slurry was concentrated and the residue reconstituted with *tert*-butyl methyl ether and stirred at 40 °C for 15 minutes. The mixture was cooled to 25 °C, filtered and the resulting solids washed with *tert*-butyl methyl ether and dried to give the title compound.

Description 27

7-(Nitromethyl)-6,7,8,9-tetrahydro-5*H*-benzo[*a*][7]annulene

A solution of 8,9-dihydro-5*H*-benzo[*a*][7]annulen-5-one (323 g, 2 mol) in nitromethane (620 ml) was treated with DBU (327 g, 2.1 mol) dropwise at such a rate that the temperature was maintained between 40 and 50 °C. After GC analysis showed reaction completion, 3M HCl (600 ml) was added and the resulting mixture was extracted with *tert*-butyl methyl ether (2 x 500 ml). The combined organic phases were treated with brine (500 ml), dried over $MgSO_4$, filtered and evaporated to an oil (496 g, 90%). To 347.5g (1.58 mol) of this material dissolved in TFA (1045 ml) was added triethylsilane (583 ml, 3.65 mol) at such a rate that the temperature of the reaction mixture was maintained between 50 and 55 °C. After the addition was complete, the mixture was maintained at 55 °C until GC analysis indicated reaction complete. The mixture

was poured onto ice (1500 g) and water (500 ml). The resulting slurry was filtered and washed with cold hexanes (2 x 150 ml) then dried to give the title compound (139 g, 42%).

Description 28

6,7,8,9-Tetrahydro-5*H*-benzo[*a*][7]annulen-7-ylmethylamine hydrochloride

A mixture of 7-(nitromethyl)-6,7,8,9-tetrahydro-5*H*-benzo[*a*][7]annulene (Description 27; 48.6 g , 0.24 mol) and Ra-Ni (50 g) in ethanol (600 ml) was hydrogenated at 60 psi for 12 hours. An additional charge of Ra-Ni (50 g) was added and the mixture was hydrogenated until GC analysis indicated the reaction was complete. The resulting mixture was filtered over Celite™ and washed with ethanol (200 ml). The filtrate was treated with concentrated HCl (35 ml, 0.42 mol) and concentrated under reduced pressure. The product was then slurried in *tert*-butyl methyl ether (100 ml) and cooled between 0 and 5°C, filtered and washed with *tert*-butyl methyl ether (100 ml) and dried to give the title compound (21 g, 42%).

Description 29

3-(1*H*-Pyrazol-1-yl)benzylamine hydrochloride

To a suspension of 3-(1*H*-pyrazol-1-yl)-benzoic acid [see WO 00/21951] (104 g, 0.55 mol) in anhydrous benzene (500 ml) was added thionyl chloride (85 g, 0.715 mol) and DMF (0.5 ml). The mixture was heated at reflux for 3 hours, then evaporated under reduced pressure. The residue was dissolved in anhydrous THF (100ml) and evaporated. The residue was dissolved in anhydrous acetone (600 ml), and treated with ammonium acetate (77 g, 1 mol). The mixture was heated at reflux for 12 hours, solvent was evaporated and the residue treated with cold water (2000 ml). The resulting precipitate was filtered, washed with cold water (200ml) and recrystallised from absolute ethanol (600 ml) to give 3-(1*H*-pyrazol-1-yl)benzamide (82 g, 80 %). A solution of this material (82 g, 0.44 mol) in THF was added dropwise to a solution of $LiAlH_4$ (25 g, 0.66 mol) in anhydrous THF (800 ml). The mixture was heated at reflux for 4 hours, cooled and quenched by the sequential addition of water (25 ml), 15% aqueous NaOH (25 ml), and water (50 ml). The inorganic by-products were filtered off and washed several times with diethyl ether (overall volume 1000 ml). The combined

filtrates were dried over Na_2SO_4, filtered and evaporated. The residue was dissolved in methanol (400 ml), the solution was treated with activated carbon (10 g), and the mixture was refluxed for 40 minutes, then filtered and evaporated. The residue was treated with 1N HCl in ether (1000 ml), and the precipitate formed was filtered, washed with ether and dried to give the title compound (53 g, 70%).

Description 30

4-(1*H*-Pyrazol-1-yl)benzylamine hydrochloride

The title compound was prepared from 4-(1*H*-pyrazol-1-yl)-benzoic acid in an analogous procedure to that detailed in Description 29.

Description 31

N-Methyl-*N*-[4-(trifluoromethyl)benzyl]amine

A mixture of 4-(trifluoromethyl)benzylamine (1.0 mL, 7.02 mmol) and di-*tert*-butyl carbonate (1.68 g, 7.72 mmol) in CH_2Cl_2 (10 mL) was stirred for 1 hour. The reaction mixture was poured into saturated aqueous ammonium chloride solution, extracted with CH_2Cl_2 and the organic layers were combined, dried over $MgSO_4$ and concentrated in vacuo to give a white crystalline solid. To a solution of the crude carbamate (1.00 g, 3.61 mmol) in THF (20 mL) in a room temperature water bath, was added $LiAlH_4$ (0.69 g, 18.1 mmol) portion-wise over 10 minutes. The reaction was then heated at reflux for 4 hours. The reaction was cooled in ice and quenched by the addition of water (1.6 mL) and NaOH (2N, 1.3 mL). The grey slurry was filtered and washed with MeOH. The MeOH was removed in vacuo and the crude product taken up in CH_2Cl_2 and dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash column chromatography eluting with 5-10 % MeOH in CH_2Cl_2 plus 1 % NH_3 solution (2N in MeOH) afforded the title compound.

Description 32

1-[4-(Trifluoromethyl)phenyl]ethylamine

To a suspension of $NaCNBH_4$ (0.48 g, 7.6 mmol) and 3Å molecular sieves (4 g) in MeOH (15 mL) was added NH_4OAc (6.15 g, 80 mmol) and 4-(trifluoromethyl)acetophenone (1.5 g, 8.0 mmol). The reaction was stirred at

room temperature under nitrogen for 3 days. The reaction was concentrated *in vacuo* and the pH adjusted to pH 12 by the addition of aqueous NaOH (2N). The reaction was extracted with ethyl acetate and the organic layers combined, dried over $MgSO_4$ and the solvent removed *in vacuo*. Purification by flash column chromatography, eluting with 5 % MeOH in CH_2Cl_2 afforded the title compound.

Description 33

1,3-Diphenylpropylamine

The title compound was prepared from 1,3-diphenylpropan-1-one in an analogous procedure to that detailed in Description 32.

Description 34

(3-Phenyl-1,2,4-oxadiazol-5-yl)methylamine hydrochloride

A mixture of 5-chloromethyl-3-phenyl-1,2,4-oxadiazole [*Synth. Commun.* 1992, 22, 209] (90 g, 0.5 mol) and potassium iodide (45 g) was added as one portion to a suspension of potassium phthalimide (90 g, 0.5 mol) in DMSO (400 ml) under intensive stirring. After self-heating ceased, the mixture was heated at 130 °C for 15 minutes, cooled, and poured into water (2.5 l). The precipitate was filtered, washed with water, and dried in the air. Recrystallization from 5% DMSO in ethanol (1 l) afforded 100 g of solid. A suspension of this solid (100 g, 0.33 mol) in ethanol (2 l) was treated with glyme (0.5 l), heated to 35-40 °C, treated with hydrazine hydrate (18 g, 0.35 mol), and heated to reflux for 2 hours. The mixture was diluted with concentrated hydrochloric acid (100 ml), and refluxed for 4 hours. After cooling the mixture was filtered, extracted with ether, and evaporated. The residue was dissolved in the minimum volume of water, basified and taken up in ether (300 ml). The organic layer was separated, dried over anhydrous magnesium sulfate, and evaporated. The residue was dissolved in the minimum volume of water, neutralized with hydrochloric acid and evaporated. The crude product was recrystallized twice from isopropanol and dried to give the title compound (21 g, 20%).

Description 35

(2-Benzyl-1,3-thiazol-4-yl)methylamine

2-Benzyl-4-chloromethylthiazole [*Pharmazie* 1972, **27**, 146] (223.7 g, 1 mol) was stirred with liquid ammonia (600 ml) in an autoclave for 24 hours. The ammonia was removed and the product was distilled *in vacuo* [bp (0.02 mmHg) 141-144°C] to give the title compound (102 g, 50%).

Description 36

[1-(2-Methylphenyl)-1*H*-pyrazol-4-yl]methylamine

A mixture of 1-(2-tolyl)-pyrazole-4-carboxaldehyde [see US Patent No. 4,220,792] (186 g, 1 mol), hydroxylamine hydrochloride (104.2 g, 1.5 mol), and sodium acetate trihydrate (204 g) in ethanol (2 l) was refluxed for 1 hour. The mixture was cooled, diluted with water (8 l), and left overnight. The precipitate was filtered to give 1-(2-tolyl)-pyrazole oxime (186 g , 92.5 %). Tolylpyrazole oxime (50.3 g, 0.25 mol) in methanol (600 ml) and ammonia (200 ml) was hydrogenated in an autoclave in the presence of Raney nickel (10 g of ethanolic suspension) at 50°C at 70 atm. The catalyst was filtered off and washed with methanol. The filtrate was evaporated, and the residue was distilled *in vacuo* to give the title compound (43 g, 92%).

Description 37

3-Cyclohexylpropylamine hydrochloride

To a solution of 3-phenyl-1-propylamine (5.26 ml, 0.04 mol) in ethanol (100 ml) under nitrogen was added concentrated HCl (3 ml) and platinum oxide (0.5 g, 0.002 mol). This was placed on a Parr apparatus and hydrogenated at 50 psi for 5 days. Platinum oxide (0.5 g, 0.002 mol) was added and the mixture hydrogenated for a further 5 days. The mixture was filtered and evaporated to give the title compound (6.4 g , 98%).

Description 38

6,7,8,9-Tetrahydro-5*H*-benzo[*a*][7]annulene-7-carboxylic acid

A solution of 7-(nitromethyl)-6,7,8,9-tetrahydro-5*H*-benzo[*a*][7]annulene (Description 27; 96 g, 0.47 mol) in THF (550 ml) was cooled to –18 °C and potassium *tert*-butoxide (1.6M in THF, 263 ml, 0.42 mol) was added dropwise

over 30 minutes while maintaining the temperature between -15 and -5 °C. After stirring for 10 minutes a solution of $KMnO_4$ (111 g, 0.7 mol) in water (900 ml) was added dropwise over 75 minutes while maintaining the temperature between -3 and 3 °C. The mixture was stirred at 0 °C until GC analysis indicated the reaction was complete. *tert*-Butyl methyl ether (500 ml) was added followed by saturated aqueous $NaHSO_3$ (1000 ml) and the resulting mixture was stirred for 30 minutes until a milky white slurry formed. This slurry was filtered, washed with a solution of 3N NaOH (50 ml) and water (100 ml) followed by *tert*-butyl methyl ether (100 ml). The pH of the filtrate was adjusted from 8.6 to 12.5 by the addition of 3N NaOH (100 ml) and 6N NaOH (40 ml). The phases were separated and to the aqueous phase was added *tert*-butyl methyl ether (500 ml). The pH of the resulting mixture was adjusted to 2 with 6N HCl (200 ml). The phases were again separated and the aqueous phase was extracted with *tert*-butyl methyl ether (2 x 300 ml). The organic phases were combined, dried over $MgSO_4$, filtered and evaporated to give the title compound (73 g, 89%), as an off white solid.

Description 39

2-Bromo-6-fluorobenzaldehyde

To a solution of diisopropylamine (15.7 ml 112 mmol) in anhydrous tetrahydrofuran (200 ml) cooled to 0 °C was added dropwise n-butyllithium (2.5M in hexanes, 44.8 ml, 112 mmol). After complete addition the mixture was cooled to –78 °C and 3-fluorobromobenzene (19.6 g, 112 mmol) added over 10 minutes. The mixture stirred at –78 °C for 1 hour then N,N dimethylformamide (9.72 ml, 125 mmol) was added dropwise over 5 minutes. The mixture was stirred for a further 10 minutes, then acetic acid (10 ml) and water (350 ml) were added. The mixture was allowed to warm to room temperature and was extracted with Et_2O (250 +150 ml). The combined extracts were washed with water (x2) 0.2N HCl, brine, dried over Na_2SO_4 and evaporated. The residue was purified by column chromatography on silica eluting with 5% Et_2O in iso-hexanes to give the title compound (20 g, 88%) as a white solid.

Description 40

2-Fluoro-6-[(trimethylsilyl)ethynyl]benzaldehyde

To a solution of 2-bromo-6-fluorobenzaldehyde (Description 39; 10.0 g, 49.3 mmol) and (trimethylsilyl) acetylene (13.94 ml, 98.6 mmol) in anhydrous N,N-dimethylformamide (250 ml) under an atmosphere of nitrogen was added triethylamine (10.25 ml, 73.95 mmol), copper (I) iodide (0.94 g, 4.93 mmol) and $Pd(PPh_3)_2Cl_2$ (1.73 g, 2.47 mmol). The mixture was degassed and stirred at room temperature overnight. The mixture was poured into water (600 ml) and extracted with ethyl acetate (3 x 200 ml). The combined organic layers were washed with water (3 x 300 ml), brine (200 ml) then dried over Na_2SO_4 and evaporated. The residue was purified by column chromatography on silica gel eluting with 5% Et_2O in iso-hexanes to give the title compound (10.38 g, 95%).

Description 41

8-Fluoroisoquinoline

2-Fluoro-6-[(trimethylsilyl)ethynyl]benzaldehyde (Description 40; 10.38 g, 47.1 mmol) was dissolved in 2M ammonia in methanol (235 ml, 471 mmol) in a Parr flask and the resulting mixture heated at 80 °C with shaking on a Parr apparatus (ca. 35 psi achieved). The reaction was cooled and the solvents evaporated. The residue was purified by column chromatography on silica eluting with a gradient from neat dichloromethane to 2% methanol in dichloromethane to give the title compound (4.0 g, 58 %).

Description 42

8-Fluoro-5-nitroisoquinoline

To a solution of 8-fluoroisoquinoline (Description 41; 1.24 g , 8.4mmol) in concentrated sulfuric acid (10 ml) cooled to between –5 °C and 0 °C was added slowly, over 10 minutes, a solution of potassium nitrate (0.93 g , 9.24 mmol) in concentrated sulfuric acid (5 ml). The mixture was stirred at 0 °C for 30 minutes after which time TLC indicated that reaction was complete. The mixture was poured onto ice (100 g) and basified by the careful addition of 33% aqueous ammonium hydroxide. The mixture was extracted with dichloromethane (3 x 150 ml) and the combined organic layers were washed with brine, dried over Na_2SO_4 and filtered through a 1 inch plug of silica gel. The silica gel plug was

further washed with 150 ml of a 1:1 mix of ethyl acetate and iso-hexanes. The combined organics were evaporated to give the title compound (1.33 g, 82%) as a brown solid.

Description 43

8-Fluoroisoquinolin-5-amine

To a nitrogen flushed solution of 8-fluoro-5-nitroisoquinoline (Description 42; 1.33 g, 6.9 mmol) in methanol (100 ml) was added 10% palladium on carbon (500 mg) and the resulting mixture stirred under a balloon of hydrogen for 3.5 hours. The catalyst was removed by filtration and the filtrate evaporated to dryness. The residue was purified by MPLC (Biotage Flash™ 40) eluting with 2% MeOH in dichloromethane to give the title compound (450 mg, 40%) as a yellow solid.

Description 44

3-Methyl-5-nitroisoquinoline

3-Methylisoquinoline (2.14 g, 14.9 mmol) was added portionwise to ice-cooled concentrated H_2SO_4 (10 ml) keeping the internal temperature below 10 °C. A nitrating mixture of concentrated H_2SO_4 (2 ml) and fuming nitric acid (2 ml) was then added dropwise keeping the internal temperature below 15 °C. After stirring for 30 minutes, TLC indicated reaction was complete. The acid was neutralized by adding the mixture to an excess of 4N aqueous NaOH (180 ml) with ice-cooling. The mixture was extracted with dichloromethane (2 x 150 ml), then dried (Na_2SO_4) and evaporated to give the crude product (2.69 g) as a yellow solid. Flash column chromatography using as eluant 5% methanol in dichloromethane gave a pure sample of the title compound (660 mg) and a further sample (1.95 g) containing ca. 10% of the isomer 3-methyl-8-nitroisoquinoline.

Description 45

3-Methylisoquinolin-5-amine

3-Methyl-5-nitroisoquinoline (Description 44; 660 mg, 3.51 mmol) was dissolved in MeOH (30 ml) and PtO_2 catalyst (120 mg) was added. The mixture was stirred for 1 hour 45 minutes under a balloon of hydrogen, then the catalyst was filtered off, washing with more methanol. The filtrate was evaporated and purified by

flash column chromatography using as eluant 5% methanol in dichloromethane to give the title compound (250 mg).

Description 46

1-Chloroisoquinoline

A solution of isoquinoline-N-oxide (5.52 g, 38 mmol) in dichloromethane (50 ml) was added over 15 minutes to a solution of phosphorus oxychloride (40 ml) in dichloromethane (50 ml) at room temperature. The mixture was stirred for 1 hour, then heated to reflux for 2 hours. After cooling to room temperature, the mixture was poured into ice water (500 ml). The mixture was then extracted with dichloromethane (2 x 250 ml) and the combined organic layers were washed with 10% aqueous potassium carbonate solution (200 ml), brine (200 ml) then dried (Na_2SO_4) and evaporated to give the title compound (5.0 g).

Description 47

1-Chloro-5-nitroisoquinoline

1-Chloroisoquinoline (Description 46; 4 g, 24.4 mmol) was nitrated according to the method of Description 44 to give the title compound (3.88 g).

Description 48

1-Chloroisoquinolin-5-amine

Copper (II) acetylacetonate (253 mg) was suspended in ethanol (10 ml) and sodium borohydride (366 mg) was added in one portion. The mixture was stirred for 5 minutes, by which time a black suspension had appeared. A suspension of 1-chloro-5-nitroisoquinoline (Description 47; 1.01 g, 4.84 mmol) in ethanol (20 ml) was then added over 15 minutes whilst cooling in a water bath; the mixture effervesced. The mixture was stirred at room temperature for 1 hour, then more sodium borohydride (160 mg) was added and stirring continued for a further 1 hour. Water (100 ml) was added then the ethanol was evaporated and the mixture extracted with ethyl acetate (3 x 50 ml). The combined organic layers were dried (Na_2SO_4) and evaporated. Purification of the residue by flash column chromatography using 5% methanol-dichloromethane as eluant gave the title compound (210 mg).

Description 49

3-Chloroisoquinoline

A mixture of 1,3-dichloroisoquinoline (9.94 g, 50.2 mmol) and hydrazine hydrate (12.2 ml, 251 mmol) in ethanol (150 ml) was heated at reflux for 1.5 hours. The reaction was then cooled to room temperature and the ethanol evaporated. The residue was suspended in chloroform and manganese dioxide (20g) was added in portions over 30 minutes. Gas evolution was observed. After this had subsided, the mixture was heated to reflux for 2 hours, then filtered and evaporated. Purification of the residue by flash column chromatography using dichloromethane as eluant gave the title compound (3.5 g).

Description 50

3-Chloroisoquinolin-5-amine

3-Chloroisoquinoline (Description 49; 3.4 g, 20.7 mmol) was nitrated according to the method of Description 44 to give crude 3-chloro-5-nitroisoquinoline (9 g). A sample (3.08 g) was added in portions over 15 minutes to a mixture of iron powder (4.2 g, 74 mmol) in water (50 ml) and 5M HCl (4 ml) at 50 °C. After the addition, the mixture was warmed to 85 °C for 2 hours, then filtered while still warm to remove the iron. The filtrate was basified (4N NaOH, ca. 50 ml), then extracted with dichloromethane (3 x 150 ml). The combined organic layers were dried (Na_2SO_4) and evaporated to give the title compound (282 mg).

Description 51

6-Aminoisoquinoline

Benzophenone imine (445 μL, 2.64 mmol) was added to a mixture of 6-bromoisoquinoline (500 mg, 2.4 mmol), BINAP (60 mg, 0.1 mmol), palladium acetate (12 mg, 0.05 mmol) and cesium carbonate (1.0 g, 3.07 mmol) in THF (10 ml) at room temperature. The mixture was degassed (N_2 x 3) then heated at reflux under a nitrogen atmosphere for 16 hours. The reaction was then cooled to room temperature, partitioned between ethyl acetate (20 ml) and water (20 ml) and the aqueous phase extracted with ethyl acetate (20 ml). The combined organic phases were evaporated then re-dissolved in THF (15 ml). Hydrochloric acid (2N, aqueous, 4 ml) was added, then after stirring for 1 hour the THF was evaporated. The mixture was partitioned between ethyl acetate (20 ml) and 3M

HCl (50 ml) and the aqueous phase washed with ethyl acetate (20 ml). The aqueous phase was basified (12N NaOH) then extracted with dichloromethane (3 x 50 ml). The combined organic phases were dried (Na_2SO_4) and evaporated to give the title compound (360 mg).

Description 52

N-(2-Bromobenzyl)-2,2-diethoxyacetamide

To a solution of ethyl diethoxyacetate (20.0g, 114 mmol) in ethanol (50 ml) was added a solution of sodium hydroxide (4.56 g, 114 mmol) in water (25 ml), and the resulting mixture heated at reflux for 5 hours. The mixture was evaporated to dryness, and the residue dried *in vacuo*. The resulting solid (22.75 g, 0.13 mol) was dissolved in dry ether (88 ml) and to this mixture was added thionyl chloride (13.3 g, 0.11 mol) with stirring for 10 minutes at 10 °C. The reaction mixture was heated at reflux for 30 minutes and then allowed to cool. A solution of 2-bromobenzylamine (20.73 g, 0.11 mol) in toluene (57 ml) and pyridine (34 ml) was poured into this reaction mixture with vigorous stirring. This was heated at reflux for 30 minutes and then allowed to cool. The mixture was poured into ice water and extracted with toluene (x 3). The organic extracts were combined and washed firstly with 2% HCl and then water. The solvent was evaporated and the residue purified by flash chromatography on silica gel (9:1 hexane:ethyl acetate) to give the title compound (15.6 g, 44%).

Description 53

8-Bromoisoquinolin-3-ol

N-(2-Bromobenzyl)-2,2-diethoxyacetamide (Description 52; 15.6 g , 49 mmol) was carefully added to concentrated H_2SO_4 (78 ml) with stirring at 10-20°C. The reaction mixture was stirred at room temperature for 16 hours, poured into ice water and filtered. The filtrate was neutralised with 33% aqueous ammonium hydroxide and the resulting precipitate was filtered and dried to give the title compound (10.1 g, 91%).

Description 54

8-Bromo-3-methoxyisoquinoline

To a suspension of 8-bromoisoquinolin-3-ol (Description 53; 7.3 g, 0.03 mol) and silver carbonate (13.6 g, 0.05 mol) in dry DMF (380 ml) under nitrogen was added iodomethane (2.25 ml, 0.04 mol). The mixture was stirred at 50 °C for 24 hours. Further iodomethane (1 ml, 0.015 mol) was added and the mixture heated for 64 hours at 50 °C. The mixture was cooled, water (300 ml) and ethyl acetate (300 ml) were added and shaken well. The mixture was filtered through Celite™, the layers separated and the aqueous layer was extracted with ethyl acetate (3 x 50 ml). The organic layers were combined, evaporated to ~150 ml, washed twice with water and then brine. The organic extract was then evaporated to give the title compound (1.7 g, 22%).

Description 55

Methyl 3-methoxyisoquinoline-8-carboxylate

To a solution of 8-bromo-3-methoxyisoquinoline (Description 54; 1.6 g, 7.0 mmol) in anhydrous DMSO (12 ml) and methanol (8 ml) was added triethylamine (1.0 ml, 7.0 mmol), palladium acetate (30 mg, 0.1 mmol) and 1,1'-bis(diphenylphosphine)ferrocene (75 mg, 0.1 mmol). Carbon monoxide was bubbled through the mixture for 3 minutes and the reaction was then heated with stirring at 80 °C for 44 hours under a balloon of carbon monoxide. Palladium acetate (30 mg, 0.1 mmol), 1,1'-bis(diphenylphosphine)ferrocene (75 mg, 0.1 mmol), DMSO (4 ml) and methanol (6 ml) were added to the mixture and carbon monoxide was bubbled through for 3 minutes. The reaction was again heated at 80 °C under a carbon monoxide balloon for 5 hours. The mixture was allowed to cool, brine (80 ml) was added and the mixture was extracted with ethyl acetate (3 x 20 ml). The combined organic layers were washed with brine (50 ml), dried over K_2CO_3 and evaporated. The residue was chromatographed on silica gel (19:1 dichloromethane: methanol) to give the title compound (290 mg, 20%).

Description 56

3-Methoxyisoquinoline-8-carboxylic acid

To a solution of methyl-3-methoxyisoquinoline-8-carboxylate (Description 55; 280 mg, 1 mmol) in ethanol (10 ml) was added potassium hydroxide (145 mg,

3 mmol) in water (6 ml). This mixture was heated at reflux for 30 minutes, cooled and the ethanol removed by evaporation. The remaining aqueous mixture was acidified with 1M HCl (3 ml) to pH 5. The solid was collected by filtration and dried in a vacuum oven to give the title compound (235 mg, 90%).

Description 57

Isoquinoline-8-carboxylic acid

THF (140 ml) was added to n-butyllithium (1.6M hexanes, 70 ml, 112 mmol) at -78 °C. A cold (-78 °C) solution of 8-bromoisoquinoline (19g, 91.3 mmol) was then added. The reaction was stirred for 15 minutes at –78 °C, then dry CO_2 gas was bubbled through the solution for 30 minutes. The cooling was then removed and the mixture warmed to 0 °C over 1 hour. The THF was removed *in vacuo*, then aqueous NaOH (2N, 300 ml) was added. The mixture was washed with *tert*-butyl methyl ether (300 ml, then 2 x 100 ml) and the combined organic layers were back extracted with aqueous NaOH (2N, 50 ml). The combined aqueous phase was adjusted to pH 4.5 by the addition of 6N HCl. And the slurry cooled to 15 °C using an ice-bath. The precipitate was collected by filtration, washed with water (2 x 100 ml), isopropanol (100 ml), acetone (100 ml) and *tert*-butyl methyl ether (100 ml) to give the title compound (8.62 g).

Description 58

[4-(Trifluoromethyl)benzyl]isocyanate

4-(Trifluoromethyl)phenylacetic acid (1.79 g, 8.77 mmol) was dissolved in dichloromethane (20 ml) at room temperature. Oxalyl chloride (0.92 ml, 10.5 mmol) was added followed by DMF (2 drops). The reaction was stirred for 4 hours, after which time effervescence had ceased. The dichloromethane and excess oxalyl chloride were then evaporated. The acid chloride was redissolved in DCM (20 ml) and poured in one go into a solution of sodium azide (0.63 g, 9.65 mmol) and tetrabutylammonium bromide (300 mg, 0.88 mmol) in water (15 ml). The mixture was stirred for 15 minutes, then the layers separated and the aqueous layer extracted with more dichloromethane (30 ml). The combined organic layers were dried (Na_2SO_4) and evaporated to give an oil which was purified by flash column (50% dichloromethane-hexane). The acyl azide (1.54 g) so produced was dissolved in dichloromethane (20 ml) and heated at reflux to

quantitatively afford the title compound. The volume was adjusted to give a 0.33 M solution in dichloromethane for use in subsequent preparations.

Description 59

[4-(Trifluoromethoxy)benzyl]isocyanate

Prepared from 4-(trifluoromethoxy)phenylacetic acid according to the method of Description 58.

Synthesis of Ureas:

Ureas were synthesized, unless otherwise stated, using one of 2 methods. A convenient procedure starts with a carboxylic acid which, on treatment with diphenylphosphoryl azide and triethylamine, undergoes a Curtius reaction. The isocyanate formed *in situ* is then trapped by addition of an amine all in one-pot. Alternatively ureas are synthesized by reacting an amine with a preformed isocyanate. Urea precursors not mentioned in Descriptions 1 to 58 are known compounds.

Description 60

Representative one-pot procedure for the synthesis of ureas from a carboxylic acid and an amine

A mixture of carboxylic acid (0.30 mmol), diphenylphosphoryl azide (65 µl, 0.30 mmol) and triethylamine (42 µl, 0.30 mmol) in toluene (5 ml) was heated at reflux for 1 hour. To this mixture, the appropriate amine (0.30 mmol) was added and the reaction heated at reflux for 18 hours. The cooled reaction mixture was evaporated to dryness, then purified either by flash column chromatography, preparative thin layer chromatography or by mass-directed HPLC. For amine hydrochloride salts, an extra equivalent of triethylamine was added.

Description 61

Representative one-pot procedure for the synthesis of ureas from an isocyanate and an amine

An amine (0.30 mmol) and an isocyanate (0.35 mmol) were dissolved in dichloromethane (10 ml), then stirred at room temperature or at reflux if required until the starting amine had been consumed. The product was collected

by filtration, washing with a little dichloromethane. In cases where the product did not crystallise out, the solvent was evaporated and purification was effected either by flash column chromatography, preparative thin layer chromatography or by mass-directed HPLC.

Description 62

3-(trifluoromethyl)isoquinoline

1-Chloro-3-(trifluoromethyl)isoquinoline [see WO 01/92233] (2.0 g, 8.64 mmol) was dechlorinated according to the method of Description 49 to give the title compound (1.42 g).

Description 63

5-nitro-3-(trifluoromethyl)isoquinoline

3-(trifluoromethyl)isoquinoline (Description 62; 1 g, 5.0 mmol) was nitrated according to the method of Description 44 to give the title compound (1.1 g).

Description 64

3-(trifluoromethyl)isoquinolin-5-amine

5-nitro-3-(trifluoromethyl)isoquinoline (Description 63; 1 g, 4.13 mmol) was hydrogenated according to the method of Description 43 to give the title compound (0.48 g).

Description 65

1-chloro-3-ethyl-5-nitroisoquinoline

1-chloro-3-ethylisoquinoline [see WO 01/92233] (2.0 g, 10.4 mmol) was nitrated according to the method of Description 42 to give the title compound (2.37 g, 96 %).

Description 66

1-chloro-3-ethylisoquinolin-5-amine

1-chloro-3-ethyl-5-nitroisoquinoline (Description 65; 2.0 g, 8.4 mmol) was reduced according to the method of Description 50 to give the title compound (1.2 g, 69 %).

Example 1

N-Benzyl-*N'*-isoquinolin-5-ylurea

Prepared from 5-aminoisoquinoline and benzyl isocyanate according to the procedure of Description 61. *m/z* (ES+) 278 (M + H)+.

Examples 2 to 16 were prepared according to the procedure of Description 60.

Example 2

N-(1,1'-Biphenyl-4-ylmethyl)-*N'*-isoquinolin-5-ylurea

Prepared from isoquinoline-5-carboxylic acid [see WO 95/09843] and 4-phenylbenzylamine. *m/z* (ES+) 354 (M + H)+.

Example 3

N-(1,1'-Biphenyl-3-ylmethyl)-*N'*-isoquinolin-5-ylurea

Prepared from isoquinoline-5-carboxylic acid and 3-phenylbenzylamine. *m/z* (ES+) 354 (M + H)+.

Example 4

N-Isoquinolin-5-yl-*N'*-(3-phenylpropyl)urea

Prepared from isoquinoline-5-carboxylic acid and 3-phenylpropylamine. *m/z* (ES+) 306 (M + H)+.

Example 5

N-Isoquinolin-5-yl-*N'*-(1,2,3,4-tetrahydronaphthalen-2-ylmethyl)urea

Prepared from isoquinoline-5-carboxylic acid and 1,2,3,4-tetrahydronaphthalen-2-ylmethylamine (Description 20). *m/z* (ES+) 332 (M + H)+.

Example 6

N-[2-(4-Chlorophenyl)ethyl]-*N'*-isoquinolin-5-ylurea

Prepared from isoquinoline-5-carboxylic acid and 2-(4-chlorophenyl)ethylamine. *m/z* (ES+) 326 (M + H)+.

Example 7

N-[3,5-bis(Trifluoromethyl)benzyl]-*N'*-isoquinolin-5-ylurea

Prepared from isoquinoline-5-carboxylic acid and 3,5-bis(trifluoromethyl)benzylamine. *m/z* (ES^+) 414 $(M + H)^+$.

Example 8

N-[3-(3,4-dimethylphenyl)propyl]-*N'*-isoquinolin-5-ylurea

Prepared from isoquinoline-5-carboxylic acid and 3-(3,4-dimethylphenyl)-propylamine. *m/z* (ES^+) 334 $(M + H)^+$.

Example 9

N-(4-*tert*-Butylbenzyl)-*N'*-isoquinolin-8-ylurea

Prepared from isoquinoline-8-carboxylic acid and 4-*tert*-butylbenzylamine. *m/z* (ES^+) 334 $(M + H)^+$.

Example 10

N-(4-*tert*-Butylbenzyl)-*N'*-isoquinolin-5-ylurea

Prepared from isoquinoline-5-carboxylic acid and 4-*tert*-butylbenzylamine. *m/z* (ES^+) 334 $(M + H)^+$.

Example 11

N-(4-*tert*-Butylbenzyl)-*N'*-quinolin-5-ylurea

Prepared from quinoline-5-carboxylic acid [see WO 95/09843] and 4-*tert*-butylbenzylamine. *m/z* (ES^+) 334 $(M + H)^+$.

Example 12

N-(3-*tert*-Butylbenzyl)-*N'*-isoquinolin-5-ylurea

Prepared from isoquinoline-5-carboxylic acid and 3-*tert*-butylbenzylamine (Description 9). *m/z* (ES^+) 334 $(M + H)^+$.

Example 13

N-[2-(4-*tert*-Butylphenyl)ethyl]-*N'*-isoquinolin-5-ylurea

Prepared from isoquinoline-5-carboxylic acid and 2-(4-*tert*-butylphenyl)ethylamine. *m/z* (ES^+) 348 $(M + H)^+$.

Example 14

N-Isoquinolin-5-yl-*N'*-[4-(trifluoromethyl)benzyl]urea

Prepared from isoquinoline-5-carboxylic acid and 4-trifluoromethylbenzylamine. *m/z* (ES+) 346 $(M + H)^+$.

Example 15

N-Isoquinolin-5-yl-*N'*-[3-(trifluoromethyl)benzyl]urea

Prepared from isoquinoline-5-carboxylic acid and 3-trifluoromethylbenzylamine. *m/z* (ES+) 346 $(M + H)^+$.

Example 16

N-Isoquinolin-5-yl-*N'*-[2-[4-(trifluoromethyl)phenyl]ethyl]urea

Prepared from isoquinoline-5-carboxylic acid and 2-[4-(trifluoromethyl)phenyl]ethylamine (Description 6). *m/z* (ES+) 360 $(M + H)^+$.

Example 17

N-(2-Oxidoisoquinolin-5-yl)-*N'*-[4-(trifluoromethyl)benzyl]urea

To a suspension of *N*-isoquinolin-5-yl-*N'*-[4-(trifluoromethyl)benzyl]urea (Example 14; 100 mg , 0.29 mmol) in chloroform (25 ml) was added Oxone (541 mg, 0.87 mmol), followed by wet alumina Grade III (1g), and the resulting suspension heated at reflux for 60 minutes. Whilst the mixture was still hot it was filtered to remove alumina and Oxone, the solids were washed with more chloroform, then methanol, and the filtrate evaporated to dryness. The residue was purified by preparative TLC eluting with 10% MeOH in dichloromethane + 0.5% NH_4OH, and the product triturated with a mixture of dichloromethane/iso-hexanes, filtered and dried to give the title compound (11 mg, 10%) as a white solid. *m/z* (ES+) 362 $(M + H)^+$.

Examples 18 to 51 were prepared according to the procedure of Description 60.

Example 18

N-Isoquinolin-5-yl-*N'*-[2-[3-(trifluoromethyl)phenyl]ethyl]urea

Prepared from isoquinoline-5-carboxylic acid and 2-[3-(trifluoromethyl)phenyl]ethylamine. *m/z* (ES^+) 360 $(M + H)^+$.

Example 19

N-Isoquinolin-5-yl-*N'*-[3-[4-(trifluoromethyl)phenyl]propyl]urea

Prepared from isoquinoline-5-carboxylic acid and 3-[4-(trifluoromethyl)phenyl]propylamine (Description 22). *m/z* (ES^+) 374 $(M + H)^+$.

Example 20

N-Isoquinolin-8-yl-*N'*-[4-(trifluoromethyl)benzyl]urea

Prepared from isoquinoline-8-carboxylic acid and 4-(trifluoromethyl)benzylamine. *m/z* (ES^+) 346 $(M + H)^+$.

Example 21

N-[3-Fluoro-4-(trifluoromethyl)benzyl]-*N'*-isoquinolin-5-ylurea

Prepared from isoquinoline-5-carboxylic acid and 3-fluoro-4-(trifluoromethyl)benzylamine. *m/z* (ES^+) 364 $(M + H)^+$.

Example 22

N-[2-Fluoro-4-(trifluoromethyl)benzyl]-*N'*-isoquinolin-5-ylurea

Prepared from isoquinoline-5-carboxylic acid and 2-fluoro-4-(trifluoromethyl)benzylamine. *m/z* (ES^+) 364 $(M + H)^+$.

Example 23

N-Isoquinolin-5-yl-*N'*-[3-[3-(trifluoromethyl)phenyl]propyl]urea

Prepared from isoquinoline-5-carboxylic acid and 3-[3-(trifluoromethyl)phenyl]propylamine (Description 23). *m/z* (ES^+) 374 $(M + H)^+$.

Example 24

N-Isoquinolin-5-yl-*N'*-[4-(trifluoromethoxy)benzyl]urea

Prepared from isoquinoline-5-carboxylic acid and 4-(trifluoromethoxy)benzylamine. *m/z* (ES+) 362 (M + H)+.

Example 25

N-{[6-(4-Fluorophenyl)pyridin-3-yl]methyl}-*N'*-isoquinolin-5-ylurea

Prepared from isoquinoline-5-carboxylic acid and [6-(4-fluorophenyl)pyridin-3-yl]methylamine (Description 25). *m/z* (ES+) 373 (M + H)+.

Example 26

N-Isoquinolin-8-yl-*N'*-{3-[4-(trifluoromethyl)phenyl]propyl}urea

Prepared from isoquinoline-8-carboxylic acid and 3-[4-(trifluoromethyl)phenyl]propylamine (Description 22). *m/z* (ES+) 374 (M + H)+.

Example 27

N-Quinolin-5-yl-*N'*-{3-[4-(trifluoromethyl)phenyl]propyl}urea

Prepared from quinoline-5-carboxylic acid and 3-[4-(trifluoromethyl)phenyl]propylamine (Description 22). *m/z* (ES+) 374 (M + H)+.

Example 28

N-Isoquinolin-8-yl-*N'*-{3-[3-(trifluoromethyl)phenyl]propyl}urea

Prepared from isoquinoline-8-carboxylic acid and 3-[3-(trifluoromethyl)phenyl]propylamine (Description 23). *m/z* (ES+) 374 (M + H)+.

Example 29

N-Quinolin-5-yl-*N'*-{3-[3-(trifluoromethyl)phenyl]propyl}urea

Prepared from quinoline-5-carboxylic acid and 3-[3-(trifluoromethyl)phenyl]propylamine (Description 23). *m/z* (ES+) 374 (M + H)+.

Example 30

N-Isoquinolin-8-yl-*N'*-[4-(trifluoromethoxy)benzyl]urea

Prepared from isoquinoline-8-carboxylic acid and 4-(trifluoromethoxy)benzylamine. *m/z* (ES+) 362 (M + H)+.

Example 31

N-Quinolin-5-yl-*N'*-[4-(trifluoromethoxy)benzyl]urea

Prepared from quinoline-5-carboxylic acid and 4-(trifluoromethoxy)benzylamine. *m/z* (ES+) 362 (M + H)+.

Example 32

N-(2,3-Dihydro-1*H*-inden-2-ylmethyl)-*N'*-isoquinolin-5-ylurea

Prepared from isoquinoline-5-carboxylic acid and 2,3-dihydro-1*H*-inden-2-ylmethylamine. *m/z* (ES+) 318 (M + H)+.

Example 33

N-Isoquinolin-5-yl-*N'*-(4-phenylcyclohexyl)urea

Prepared from isoquinoline-5-carboxylic acid and 4-phenylcyclohexylamine. *m/z* (ES+) 346 (M + H)+.

Example 34

N-Isoquinolin-5-yl-*N'*-(6,7,8,9-tetrahydro-5*H*-benzo[*a*][7]annulen-6-ylmethyl)urea

Prepared from isoquinoline-5-carboxylic acid and 6,7,8,9-tetrahydro-5*H*-benzo[*a*][7]annulen-6-ylmethylamine hydrochloride (Description 26). *m/z* (ES+) 346 (M + H)+.

Example 35

N-Isoquinolin-5-yl-*N'*-(6,7,8,9-tetrahydro-5*H*-benzo[*a*][7]annulen-7-ylmethyl)urea

Prepared from isoquinoline-5-carboxylic acid and 6,7,8,9-tetrahydro-5*H*-benzo[*a*][7]annulen-7-ylmethylamine hydrochloride (Description 28). *m/z* (ES+) 346 (M + H)+.

Example 36

N-isoquinolin-5-yl-*N'*-{[5-(trifluoromethyl)pyridin-2-yl]methyl}urea

Prepared from isoquinoline-5-carboxylic acid and 2-aminomethyl-5-(trifluoromethyl)pyridine (Description 2). *m/z* (ES+) 347 (M + H)+.

Example 37

N-[(4-*tert*-Butylpyridin-2-yl)methyl]-*N'*-isoquinolin-5-ylurea

Prepared from isoquinoline-5-carboxylic acid and 2-aminomethyl-4-*tert*-butylpyridine (Description 5). *m/z* (ES+) 335 (M + H)+.

Example 38

N-[(6-*tert*-Butylpyridin-3-yl)methyl]-*N'*-isoquinolin-5-ylurea

Prepared from isoquinoline-5-carboxylic acid and 3-aminomethyl-6-*tert*-butylpyridine (Description 11). *m/z* (ES+) 335 (M + H)+.

Example 39

N-[(2-*tert*-Butylpyridin-4-yl)methyl]-*N'*-isoquinolin-5-ylurea

Prepared from isoquinoline-5-carboxylic acid and 4-aminomethyl-2-*tert*-butylpyridine (Description 13). *m/z* (ES+) 335 (M + H)+.

Example 40

N-[(6-*tert*-Butylpyridin-2-yl)methyl]-*N'*-isoquinolin-5-ylurea

Prepared from isoquinoline-5-carboxylic acid and 2-aminomethyl-6-*tert*-butylpyridine (Description 16). *m/z* (ES+) 335 (M + H)+.

Example 41

N-Isoquinolin-5-yl-*N'*-{[6-(trifluoromethyl)pyridin-3-yl]methyl}urea

Prepared from isoquinoline-5-carboxylic acid and 3-aminomethyl-6-(trifluoromethyl)pyridine. *m/z* (ES+) 347 (M + H)+.

Example 42

N-Isoquinolin-5-yl-*N'*-{3-[6-(trifluoromethyl)pyridin-3-yl]propyl}urea

Prepared from isoquinoline-5-carboxylic acid and 3-[6-(trifluoromethyl)pyridin-3-yl]propylamine (Description 18). *m/z* (ES+) 375 (M + H)+.

Example 43

N-Isoquinolin-5-yl-*N'*-[3-(1*H*-pyrazol-1-yl)benzyl]urea

Prepared from isoquinoline-5-carboxylic acid and 3-(1*H*-pyrazol-1-yl)benzylamine hydrochloride (Description 29). *m/z* (ES+) 344 $(M + H)^+$.

Example 44

N-Isoquinolin-5-yl-*N'*-[4-(1*H*-pyrazol-1-yl)benzyl]urea

Prepared from isoquinoline-5-carboxylic acid and 4-(1*H*-pyrazol-1-yl)benzylamine hydrochloride (Description 30). *m/z* (ES+) 344 $(M + H)^+$.

Example 45

N-Isoquinolin-5-yl-*N'*-[(2-phenyl-1,3-thiazol-5-yl)methyl]urea

Prepared from isoquinoline-5-carboxylic acid and (2-phenyl-1,3-thiazol-5-yl)methylamine. *m/z* (ES+) 361 $(M + H)^+$.

Example 46

N-Isoquinolin-5-yl-*N'*-[(2-thien-2-yl-1,3-thiazol-4-yl)methyl]urea

Prepared from isoquinoline-5-carboxylic acid and (2-thien-2-yl-1,3-thiazol-4-yl)methylamine. *m/z* (ES+) 367 $(M + H)^+$.

Example 47

N-Isoquinolin-5-yl-*N'*-[(4-phenyl-1,3-thiazol-2-yl)methyl]urea

Prepared from isoquinoline-5-carboxylic acid and (4-phenyl-1,3-thiazol-2-yl)methylamine. *m/z* (ES+) 361 $(M + H)^+$.

Example 48

N-Isoquinolin-5-yl-*N'*-[(2-phenyl-1,3-thiazol-4-yl)methyl]urea

Prepared from isoquinoline-5-carboxylic acid and (2-phenyl-1,3-thiazol-4-yl)methylamine. *m/z* (ES+) 361 $(M + H)^+$.

Example 49

N-Isoquinolin-5-yl-*N'*-[2-(4-phenyl-1,3-thiazol-2-yl)ethyl]urea

Prepared from isoquinoline-5-carboxylic acid and 2-(4-phenyl-1,3-thiazol-2-yl)ethylamine. *m/z* (ES^+) 375 $(M + H)^+$.

Example 50

N-Isoquinolin-5-yl-*N'*-[(5-phenylisoxazol-3-yl)methyl]urea

Prepared from isoquinoline-5-carboxylic acid and (5-phenylisoxazol-3-yl)methylamine. *m/z* (ES^+) 345 $(M + H)^+$.

Example 51

N-Isoquinolin-5-yl-*N'*-[(3-phenylisoxazol-5-yl)methyl]urea

Prepared from isoquinoline-5-carboxylic acid and (3-phenylisoxazol-5-yl)methylamine. *m/z* (ES^+) 345 $(M + H)^+$.

Example 52

N-(8-Fluoroisoquinolin-5-yl)-*N'*-[4-(trifluoromethyl)benzyl]urea

Prepared from 8-fluoroisoquinolin-5-amine (Description 43) and [4-(trifluoromethyl)benzyl]isocyanate (Description 58) according to the procedure of Description 61. *m/z* (ES^+) 364 $(M + H)^+$.

Example 53

N-Isoquinolin-5-yl-*N*-methyl-*N'*-[4-(trifluoromethyl)benzyl]urea

Sodium hydride (60 % dispersion in oil, 7 mg, 0.17 mmol) was added to a suspension *N*-isoquinolin-5-yl-*N'*-[4-(trifluoromethyl)benzyl]urea (Example 14; 48 mg, 0.14 mmol) in THF (3 mL) at room temperature and the reaction was stirred until effervescence ceased (20 minutes). Methyl iodide (11 µL, 0.17 mmol) was added and the reaction stirred at room temperature for 3 hours. TLC analysis (10 % MeOH in CH_2Cl_2) indicated only one major product. The reaction was evaporated *in vacuo* and the product isolated by preparative TLC (4 % MeOH in CH_2Cl_2) to give the title compound. *m/z* (ES^+) 360 $(M + H)^+$.

Examples 54 to 60 were prepared according to the procedure of Description 60.

Example 54

N'-Isoquinolin-5-yl-*N*-methyl-*N*-[4-(trifluoromethyl)benzyl]urea

Prepared from isoquinoline-5-carboxylic acid and *N*-methyl-*N*-[4-(trifluoromethyl)benzyl]amine (Description 31). *m/z* (ES^+) 190 $(M + H)^+$.

Example 55

N-Isoquinolin-5-yl-*N'*-{1-[4-(trifluoromethyl)phenyl]ethyl}urea

Prepared from isoquinoline-5-carboxylic acid and 1-[4-(trifluoromethyl)phenyl]ethylamine (Description 32). *m/z* (ES^+) 360 $(M + H)^+$.

Example 56

N-(1,3-Diphenylpropyl)-*N'*-isoquinolin-5-ylurea

Prepared from isoquinoline-5-carboxylic acid and 1,3-diphenylpropylamine (Description 33). *m/z* (ES^+) 382 $(M + H)^+$.

Example 57

N-Isoquinolin-5-yl-*N'*-[(3-phenyl-1,2,4-oxadiazol-5-yl)methyl]urea

Prepared from isoquinoline-5-carboxylic acid and (3-phenyl-1,2,4-oxadiazol-5-yl)methylamine hydrochloride (Description 34). *m/z* (ES^+) 346 $(M + H)^+$.

Example 58

N-[(2-Benzyl-1,3-thiazol-4-yl)methyl]-*N'*-isoquinolin-5-ylurea

Prepared from isoquinoline-5-carboxylic acid and 2-benzyl-1,3-thiazol-4-yl)methylamine (Description 35). *m/z* (ES^+) 375 $(M + H)^+$.

Example 59

N-Isoquinolin-5-yl-*N'*-{[1-(2-methylphenyl)-1*H*-pyrazol-4-yl]methyl}urea

Prepared from isoquinoline-5-carboxylic acid and [1-(2-methylphenyl)-1*H*-pyrazol-4-yl]methylamine (Description 36). *m/z* (ES^+) 358 $(M + H)^+$.

Example 60

N-(3-Methoxyisoquinolin-8-yl)-*N'*-[4-(trifluoromethyl)benzyl]urea

Prepared from 3-methoxyisoquinoline-8-carboxylic acid (Description 56) and 4-(trifluoromethyl)benzylamine. *m/z* (ES^+) 376 $(M + H)^+$.

Example 61

N-Cinnolin-5-yl-*N'*-[4-(trifluoromethyl)benzyl]urea

Prepared from cinnolin-5-amine (*Sci Pharm.* 1982, **50**, 246) and [4-(trifluoromethyl)benzyl]isocyanate (Description 58) according to the procedure of Description 61. *m/z* (ES^+) 347 $(M + H)^+$.

Examples 62 to 64 were prepared according to the procedure of Description 60.

Example 62

N-(4-*tert*-Butylbenzyl)-*N'*-cinnolin-5-ylurea

Prepared from cinnolin-5-amine (*Sci Pharm.* 1982, **50**, 246) and (4-*tert*-butylbenzyl)acetic acid. *m/z* (ES^+) 335 $(M + H)^+$.

Example 63

N-(3-Cyclohexylpropyl)-*N'*-isoquinolin-5-ylurea

Prepared from isoquinoline-5-carboxylic acid and 3-cyclohexylpropylamine hydrochloride (Description 37). *m/z* (ES^+) 312 $(M + H)^+$.

Example 64

N-Isoquinolin-5-yl-*N'*-(6,7,8,9-tetrahydro-5*H*-benzo[*a*][7]annulen-7-yl)urea

Prepared from isoquinolin-5-amine and 6,7,8,9-tetrahydro-5*H*-benzo[*a*][7]annulene-7-carboxylic acid (Description 38). *m/z* (ES^+) 332 $(M + H)^+$.

Example 65

N-Isoquinolin-5-yl-*N'*-[4-(trifluoromethyl)benzyl]thiourea

To a solution of 1,1'-thiocarbonyldi-2(1*H*)-pyridone (330 mg, 1.4 mmol) in dichloromethane (13 ml) under nitrogen was added, dropwise, a solution of 4-(trifluoromethyl)benzylamine (200 µl, 1.4 mmol) in dichloromethane (10 ml). The solution was stirred at room temperature for 16 hours. 5-Aminoisoquinoline

(245 mg, 0.0017 mol) was added to the reaction mixture, which was then heated at reflux for 2 days and evaporated. Preparative TLC (eluant 5% methanol/ 95% dichloromethane) gave a product band also containing 5-aminoisoquinoline. The mixed product (230 mg) was dissolved in acetonitrile (40 ml) and tetrafluorophthalic anhydride (700 mg, 3.2 mmol) was added. The reaction was stirred at room temperature for 16 hours. Ethyl acetate (60 ml) was added to the reaction mix which was then washed with saturated aqueous sodium bicarbonate (3 x 20 ml). The organic extract was evaporated and the residue purified by preparative TLC (eluant system 5% methanol/ 95% dichloromethane) to give the title compound (77 mg, 23%). *m/z* (ES^+) 362 $(M + 1)^+$.

Example 66

N-Isoquinolin-6-yl-*N'*-[4-(trifluoromethyl)benzyl]urea

Prepared from 6-aminoisoquinoline (Description 51) and [4-(trifluoromethyl)benzyl]isocyanate (Description 58) according to the procedure of Description 61. *m/z* (ES^+) 346 $(M + H)^+$.

Example 67

N-Isoquinolin-6-yl-*N'*-[4-(trifluoromethoxy)benzyl]urea

Prepared from 6-aminoisoquinoline (Description 51) and [4-(trifluoromethoxy)benzyl]isocyanate (Description 59) according to the procedure of Description 61. *m/z* (ES^+) 362 $(M + H)^+$.

Example 68

N-(3-Methylisoquinolin-5-yl)-*N'*-[4-(trifluoromethyl)benzyl]urea

Prepared from 3-methylisoquinolin-5-amine (Description 45) and [4-(trifluoromethyl)benzyl]isocyanate (Description 58) according to the procedure of Description 61. *m/z* (ES^+) 360 $(M + H)^+$.

Example 69

N-(1-Chloroisoquinolin-5-yl)-*N'*-[4-(trifluoromethyl)benzyl]urea

Prepared from 1-chloroisoquinolin-5-amine (Description 48) and [4-(trifluoromethyl)benzyl]isocyanate (Description 58) according to the procedure of Description 61. *m/z* (ES^+) 380, 382 $(M + H)^+$.

Example 70

N-[1-(Dimethylamino)isoquinolin-5-yl]-*N'*-[4-(trifluoromethyl)benzyl]urea

N-(1-Chloroisoquinolin-5-yl)-*N'*-(4-trifluoromethylbenzyl)urea (Example 69; 60 mg) was suspended in ethanol (5 ml). Ethanolic dimethylamine (33%, 2 ml) was added and the mixture heated to 100 °C in a sealed tube for 16 hours after which time TLC indicated complete reaction. The reaction mixture was evaporated and the residue purified by preparative thin layer chromatography (5% methanol-dichloromethane eluant) to give the title compound (20 mg). *m/z* (ES+) 389 $(M + H)^+$.

Example 71

N-(3-Methylisoquinolin-5-yl)-*N'*-[4-(trifluoromethoxy)benzyl]urea

Prepared from 3-methylisoquinolin-5-amine (Description 45) and [4-(trifluoromethoxy)benzyl]isocyanate (Description 59) according to the procedure of Description 61. *m/z* (ES+) 376 $(M + H)^+$.

Example 72

N-(3-Methylisoquinolin-8-yl)-*N'*-[4-(trifluoromethyl)benzyl]urea

A sample of 3-methyl-5-nitroisoquinoline (Description 44) enriched in the nitration byproduct 3-methyl-8-nitroisoquinoline was reduced according to Description 45 and the mixture of amines reacted with [4-(trifluoromethyl)benzyl]isocyanate (Description 58) according to the procedure of Description 61. Isomer separation of the products gave the title compound. *m/z* (ES+) 360 $(M + H)^+$.

Example 73

N-(3-Chloroisoquinolin-5-yl)-*N'*-[4-(trifluoromethyl)benzyl]urea

Prepared from 3-chloroisoquinolin-5-amine (Description 50) and [4-(trifluoromethyl)benzyl]isocyanate (Description 58) according to the procedure of Description 61. *m/z* (ES+) 380, 382 $(M + H)^+$.

Example 74

N-(3-Methylcinnolin-5-yl)-*N'*-[4-(trifluoromethyl)benzyl]urea

Prepared from 3-methylcinnolin-5-amine and [4-(trifluoromethyl)benzyl]isocyanate (Description 58) according to the procedure of Description 61. *m/z* (ES+) 361 $(M + H)^+$.

Example 75

N-Cinnolin-5-yl-*N'*-[4-(trifluoromethoxy)benzyl]urea

Prepared from cinnolin-5-amine [*Sci Pharm.* 1982, **50**, 246] and [4-(trifluoromethoxy)benzyl]isocyanate (Description 59) according to the procedure of Description 61. *m/z* (ES+) 363 $(M + H)^+$.

Example 76

N-(1-hydroxyisoquinolin-5-yl)-*N'*-[4-(trifluoromethyl)benzyl]urea

N-(1-chloroisoquinolin-5-yl)-*N'*-[4-(trifluoromethyl)benzyl]urea (Example 69; 47 mg, 0.12 mmol) was added to a mixture of 3N HCl (aq. 5 ml) and THF (1 ml). The mixture was heated at 90 °C for 20 hours, then 5N HCl (aq. 2 ml) was added and the reaction heated at 90 °C for a further 20 hours. After cooling to room temperature, ethyl acetate (20 ml) was added and the layers separated (some solid was suspended in the organic layer). The organic phase was washed with saturated aqueous $NaHCO_3$ (20 ml), then evaporated. The residue was triturated in refluxing isopropyl alcohol (5 ml), then cooled to room temperature. The white solid was collected by filtration and washed with isopropyl alcohol (2 x 1 ml) to give the title compound (22 mg). *m/z* (ES+) 362 $(M + H)^+$.

Example 77

N-[4-(trifluoromethyl)benzyl]-*N'*-[3-(trifluoromethyl)isoquinolin-5-yl]urea

Prepared from 3-(trifluoromethyl)isoquinolin-5-amine (Description 64) and [4-(trifluoromethyl)benzyl]isocyanate (Description 58) according to the procedure of Description 61. *m/z* (ES+) 414 $(M + H)^+$.

Example 78

N-(1-chloro-3-ethylisoquinolin-5-yl)-*N'*-[4-(trifluoromethyl)benzyl]urea

Prepared from 1-chloro-3-ethylisoquinolin-5-amine (Description 66) and [4-(trifluoromethyl)benzyl]isocyanate (Description 58) according to the procedure of Description 61. *m/z* (ES^+) 408 , 410 $(M + H)^+$.

The following quinolin-6-yl derivatives were also prepared by similar methodology:

Example 79

N-phenyl-*N'*-[quinolin-6-yl]urea

Prepared from 6-aminoquinoline and phenyl isocyanate. *m/z* (ES^+) 264 $(M + H)^+$.

Example 80

N-(2-naphthyl)-*N'*-[quinolin-6-yl]urea

Prepared from 6-aminoquinoline and 2-naphthyl isocyanate.
m/z (ES^+) 314 $(M + H)^+$.

Example 81

N-(4-nitrophenyl)-*N'*-[quinolin-6-yl]urea

Prepared from 6-aminoquinoline and 4-nitrophenyl isocyanate.
m/z (ES^+) 309 $(M + H)^+$.

Example 82

N-[3,5-bis(trifluoromethyl)phenyl]-*N'*-[quinolin-6-yl]urea

Prepared from 6-aminoquinoline and 3,5-bis(trifluoromethyl)phenyl isocyanate.
m/z (ES^+) 400 $(M + H)^+$.

Example 83

N-(4-phenoxyphenyl)-*N'*-[quinolin-6-yl]urea

Prepared from 6-aminoquinoline and 4-phenoxyphenyl isocyanate.
m/z (ES^+) 356 $(M + H)^+$.

Example 84

N-(4-acetylphenyl)-*N'*-[quinolin-6-yl]urea

Prepared from 6-aminoquinoline and 4-acetylphenyl isocyanate.

m/z (ES+) 306 (M + H)+.

Example 85

N-benzyl-*N'*-[quinolin-6-yl]urea

Prepared from 6-aminoquinoline and benzyl isocyanate. *m/z* (ES+) 278 (M + H)+.

Example 86

N-[quinolin-6-yl]-*N'*-[4-(trifluoromethoxy)phenyl]urea

Prepared from 6-aminoquinoline and 4-(trifluoromethoxy)phenyl isocyanate.

m/z (ES+) 348 (M + H)+.

Example 87

N-(4-cyanophenyl)-*N'*-[quinolin-6-yl]urea

Prepared from 6-aminoquinoline and 4-cyanophenyl isocyanate.

m/z (ES+) 289 (M + H)+.

Example 88

N-(1,1'-biphenyl-4-yl)-*N'*-[quinolin-6-yl]urea

Prepared from 6-aminoquinoline and 4-biphenyl isocyanate.

m/z (ES+) 340 (M + H)+.

Example 89

N-[4-(dimethylamino)phenyl]-*N'*-[quinolin-6-yl]urea

Prepared from 6-aminoquinoline and 4-(dimethylamino)phenyl isocyanate.

m/z (ES+) 307 (M + H)+.

Example 90

N-(1,3-benzodioxol-5-yl)-*N'*-[quinolin-6-yl]urea

Prepared from 6-aminoquinoline and 3,4-(methylenedioxy)phenyl isocyanate.

m/z (ES+) 308 (M + H)+.

Example 91

N-cyclohexyl-*N'*-[quinolin-6-yl]urea

Prepared from 6-aminoquinoline and cyclohexyl isocyanate.

m/z (ES+) 270 $(M + H)^+$.

Example 92

N-[(+/-)-1-phenylethyl]-*N'*-[quinolin-6-yl]urea

Prepared from 6-aminoquinoline and (+/-)-1-phenylethyl isocyanate.

m/z (ES+) 292 $(M + H)^+$.

The above exemplified compounds of the present invention have been tested in the following assay and generally possess an $IC_{50} < 1$ μM and, in the majority of cases, < 200 nM.

Biological Methodology

Determination of *in vitro* activity

CHO cells, stably expressing recombinant human VR1 receptors and plated into black-sided 384-well plates, were washed twice with assay buffer (Hepes-buffered saline) and then incubated with 1uM Fluo-3-AM for 60 minutes in darkness. Cells were washed twice more to remove excess dye, before being placed, along with plates containing capsaicin and test compounds in a Molecular Devices FLIPR. The FLIPR simultaneously performed automated pharmacological additions and recorded fluorescence emmission from Fluo-3. In all experiments, basal fluorescence was recorded, before addition of test compounds and subsequent addition of a previously determined concentration of capsaicin that evoked 80% of the maximum respsonse. Inhibition of capsaicin evoked increases in intracellular $[Ca^{2+}]$ were expressed relative to wells on the same plate to which capcaicin was added in the absence of test compounds. Increases in intracellular $[Ca^{2+}]$ occuring after addition of test compound alone, prior to addition of capsaicin, allow determination of intrinsic agonist or partial agonist activity, if present.

Determination of *in vivo* efficacy in a capsaicin paw flinch model

(Method adapted from Taniguchi *et al*, 1997, *Br J Pharmacol.* 122(5):809-12)

To determine *in vivo* functional occupancy of VR1 receptors, compounds are administered orally to male Sprague Dawley rats typically 1 hour prior to receiving an intraplantar injection of capsaicin (2µg dissolved in ethanol) and the number of flinches of the injected paw is recorded for 5 minutes immediately thereafter. Statistical analysis is performed using one-way ANOVA followed by Dunnett's test; p values <0.05 compared to capsaicin/vehicle-treated rats are considered significant.

Determination of *in vivo* efficacy in a model of inflammatory pain

(Method adapted from Hargreaves *et al*, 1988 *Pain*, 32(1):77-88).

Antinociceptive activity is determined using a rat carrageenan-induced thermal hyperalgesia assay. Inflammatory hyperalgesia is induced by intraplantar injection of carrageenan (lambda-carrageenan 0.1 ml of 1% solution made up in saline) into one hind paw. Compounds are given orally typically 2 hours after carrageenan and paw withdrawal latancies determined 1 hour later. Paw withdrawal latencies to application of noxious thermal stimuli to plantar surface of the hind paw are measured using the Hargreaves apparatus. Thermal hyperalgesia is defined as the difference in paw withdrawal latencies for saline/vehicle- and carrageenan/vehicle-treated rats. Paw wthdrawal latencies for drug treated rats are expressed as a percentage of this response. Statistical analysis is performed using one-way ANOVA followed by Dunnett's test; p values <0.05 compared to carrageenan/vehicle-treated rats are considered significant.